CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761178Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 106230

MEETING MINUTES

Biogen, Inc.
Attention: Priya Singhal, MD, MPH
Senior Vice President, Global Safety and Regulatory Sciences
225 Binney St.
Cambridge, MA 02142

Dear Dr. Singhal:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for aducanumab.

We also refer to the teleconference between representatives of your firm and the FDA on June 17, 2020. The purpose of the meeting was to discuss the development plan for aducanumab.

A copy of the official minutes of the meeting/teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact E. Andrew Papanastasiou, Regulatory Project Manager, by email at emilios.papanastasiou@fda.hhs.gov or by phone at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Acting Director
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: June 17, 2020, from 11:00 AM to 1:00 PM

Application Number: IND 106230
Product Name: aducanumab (BIIB037, anti-Aβ monoclonal antibody)
Indication: Alzheimer's disease
Sponsor Name: Biogen, Inc.
Regulatory Pathway: 351(a)

FDA ATTENDEES

Billy Dunn, MD	Director, Office of Neuroscience
Eric Bastings, MD	Acting Director, Division of Neurology 1 (DN1)
Teresa Buracchio, MD	Acting Deputy Director, DN1
Nicholas Kozauer, MD	Acting Director, Division of Neurology 2 (DN2)
Ranjit Mani, MD	Clinical Team Leader, DN1
Brian Trummer, MD, PhD	Clinical Reviewer, DN1
Kevin Krudys PhD	Senior Clinical Analyst, DN1
Kun Jin, PhD	Biostatistics Team Leader
Tristan Massie, PhD	Statistical Reviewer
Sue Jane Wang, PhD	Associate Office Director, Biometrics I
Hsien Ming (Jim) Hung, PhD	Director, Division of Biometrics I
Sally Jo Yasuda, MS, PharmD	Safety Team Leader
Natalie Branagan, MD	Safety Reviewer, DN1
Emilios Andrew Papanastasiou, MS, PharmD	Senior Regulator Project Manager, Division of Regulatory Operations for Neuroscience (DRON)
Daniel Ngembus, PharmD	Regulatory Project Manager, DRON
Gopichand Gottipati, PhD	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)

SPONSOR ATTENDEES

Al Sandrock	Executive Vice President, Chief Medical Officer
Samantha Budd Haeberlein	VP, Clinical Development
Christian von Hehn	Medical Director, Clinical Development
Carmen Castrillo-Viguera	Medical Director, Clinical Development
Spyros Chalkias	Medical Director, Drug Safety

Angela Neufeld	Director, Global Regulatory Sciences
Helen Lockett	Director, EU Regulatory Sciences
Ying Zhu	Distinguished Biostatistician
Ying Tian	Director, Biostatistics
Tianle Chen	Principal Biostatistician
Craig Mallinckrodt	Senior Director, Biostatistics
Shuang Wu	Associate Director, Biostatistics
Xiaopeng Miao	Associate Director, Biostatistics
Laura Nisenbaum	Senior Director, Diagnostic Pathways
Raj Rajagovindan	Associate Director, Development Imaging
Ivan Nestorov	Senior Director, Pharmacometrics
Kumar Kandadi Muralidharan	Associate Director, Pharmacometrics
LeAnne Skordos	Director, Clinical Program Leadership
Liz Miller	Associate Director, Medical Writing
Kate Hecht	Sr. Director, Business Strategy and Leadership
Martin Rabe	Eisai
Michael Irizarry	Eisai

1.0 BACKGROUND

The overall purpose of this Type C meeting is to discuss the efficacy and safety data that are currently available for aducanumab (BIIB037) in the context of a planned Biologics License Application (BLA) for that compound. Aducanumab is a humanized monoclonal antibody to β-amyloid. The currently-proposed indication for aducanumab is (b) (4)

Two Phase 3 studies, 221AD301 (Study 301) and 221AD302 (Study 302), that were identical in design have been conducted with aducanumab. The primary objective of each study was to evaluate the efficacy of monthly doses of aducanumab in the treatment of patients with early Alzheimer's disease; each was a randomized, double-blind, placebo-controlled, parallel-arm study with an initial placebo-controlled period of 78 weeks to be followed by a long-term extension up to 5 years. The primary efficacy parameter was the change from baseline to Week 78 in Clinical Dementia Rating Scale – Sum of Boxes score. Secondary efficacy parameters included the change from baseline to Week 78 in Mini-Mental Status Examination, 13-item Alzheimer's Disease Assessment Scale – Cognitive, and Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale scores. Biomarker-based outcome measures were to include: amyloid positron emission tomographic signal; several measures derived from volumetric brain magnetic resonance imaging; and others. Safety measures were to include adverse events, vital signs, electrocardiograms, safety laboratory tests, anti-aducanumab antibody titers, brain MRI, and a suicidality assessment.

Studies 301 and 302 were discontinued on March 21, 2019, after a prespecified interim futility analysis indicated that the prespecified criteria for futility were met and that those

studies were unlikely to meet their primary endpoint on completion. The interim analysis of futility included all data available as of December 26, 2018, for all study patients randomized at least 78 weeks prior to that date. The results of that analysis led to both studies being discontinued on March 21, 2019.

Subsequent efficacy analyses, based on data available through March 20, 2019, had yielded results that questioned the earlier assessment of futility. Those subsequent efficacy analyses and the next steps to be taken were discussed at a face-to-face Type C meeting between the Agency and sponsor on June 14, 2019. At that meeting, it was recommended to the sponsor that further analyses of the efficacy data for Studies 301 and 302 be conducted under a collaborative workstream between the Agency and sponsor.

After the Type C meeting on June 14, 2019, additional analyses of the results of Studies 301 and 302 were conducted jointly by the Agency and sponsor under a collaborative workstream. Those analyses have been conducted in two waves first agreed upon at a meeting held on July 2, 2019:

- Wave 1: To determine whether early termination of Studies 301 and 302 may have impacted the interpretation of efficacy data for those studies and to determine which dataset was appropriate to use for the additional analyses to be conducted in Wave 2.

- Wave 2: To understand the consistency of and differences in the efficacy results of Studies 301 and 302.

After the Waves 1 and 2 analyses were completed, they were further discussed between the Agency and sponsor at a face-to-face Type C meeting held on October 21, 2019. Please see the minutes of that meeting for full details of what was discussed at that time.

Subsequent to that meeting, and in extension of the Wave 1 and 2 analyses, the collaborative workstream then sought to address additional questions generated during the Wave 2 analyses; that additional effort was termed “Wave 2+,” the aims of which were as follows:

1. To use propensity score matching to supplement previous work assessing whether subgroups in Study 301 had outcomes similar to the overall results in Study 302. Wave 2 utilized unmatched placebo groups and placebo groups matched on apolipoprotein E ε4 (ApoE ε4) carrier status and enrollment timing.

2. To further characterize the dose-exposure-response relationship.

3. To refine and extend pharmacokinetic-pharmacodynamic models through use of the additional data available in the final database.

4. To characterize associations between changes in amyloid beta positron emission tomography standardized uptake value ratio (Aβ PET SUVR) and clinical outcomes.

The additional analyses subsumed under Wave 2+ used data not only from Studies 301 and 302, but also from a Phase 1b randomized, double-blind, placebo-controlled study 221AD103 (Study 103). The results of those analyses and their implications were discussed at a further Type C meeting held between the Agency and sponsor on February 27, 2020. Please see the minutes of that meeting for further details.

Subsequent to the meeting on February 27, 2020, there have been further interactions between the Agency and sponsor as part of the aforementioned collaborative workstream.

The results of the analyses described above, other efficacy-related analyses, and analyses of safety data for aducanumab have been summarized in full in the meeting package submitted by the sponsor. As stated in this meeting package, the sponsor "seeks to discuss the primary basis for effectiveness for the intended BLA submission and the safety profile of aducanumab, especially focusing on amyloid-related imaging abnormalities (ARIA), the adverse event (AE) of special interest."

On June 8, 2020, subsequent to the submission of this Type C meeting package, the sponsor submitted a Pre-BLA meeting package. While a formal Pre-BLA meeting between the Agency and sponsor has been scheduled for July 8, 2020, the sponsor has also stated in the cover letter to that submission an openness to the Agency responding to the contents of that submission with written responses only. Topics covered in the Pre-BLA meeting package regarding which the sponsor has sought Agency advice include the following: the need for a post-BLA safety update; a proposal for the submission of patient case report forms and narratives; a proposal for a Communication Risk Evaluation and Mitigation Strategy (REMS) program addressing ARIA; the proposed Study Data Standardization Plan (SDSP); the terms that might be used to describe patients enrolled in the aducanumab clinical trials in the US Prescribing Information; whether the planned BLA may qualify for a priority review; and whether that application may need discussion at a meeting of the Peripheral and Central Nervous System Drug Advisory Committee. For the reasons noted below (see ADDITIONAL PRE-BLA COMMENTS), the questions in that meeting package are also addressed in this letter.

FDA sent Preliminary Comments to Biogen on June 12, 2020.

2.0 DISCUSSION

Question 1: Does the Agency agree that Study 302 is a positive trial in the study population on its prespecified primary endpoint with support from secondary and

biomarker endpoints in the context of Wave 1, and will provide the primary evidence in support of the effectiveness of aducanumab?

FDA Response to Question 1:
The Wave 1 analysis established that early termination of Study 302 and Study 301 did not compromise the interpretability of the results of those studies. Therefore, the results of Study 302 appear reliable and on face represent a positive trial with support from secondary and biomarker endpoints. Considering that the Wave 1 analysis also established Study 301 as a negative study, it follows that Study 302 would serve as the primary source of evidence in support of the effectiveness of aducanumab in a marketing application.

Discussion:
See the discussion under Question 3.

Question 2: Does the Agency agree that Wave 2 and Wave 2+ provide additional data from Study 301 that further supports the understanding of the effectiveness of aducanumab as demonstrated in Study 302?

FDA Response to Question 2:
As noted in the minutes of the Type C meeting held between the Agency and you on February 27, 2020, the Wave 2 and Wave 2+ analyses may help provide an overall understanding of the efficacy data for aducanumab and will be considered in terms of their ability to support or undermine the independent results of Study 302. The analyses do not, however, appear capable of providing independent evidence of effectiveness. The extent to which those analyses support or undermine the results of Study 302 will be a matter of review.

Discussion:
See the discussion under Question 3.

Question 3: In light of Question 1 and Question 2, does the Agency agree that the results of Study 302 form the basis of a demonstration of substantial evidence of effectiveness of aducanumab in the context of the submission with supportive understanding provided by Study 301, Study 103, Wave 2 and Wave 2+?

FDA Response to Question 3:
Please see our responses to Questions 1 and 2. The circumstances under which a single adequate and well-controlled study (Study 302) can be used as the sole basis for demonstrating the efficacy of a drug or biologic are discussed in the draft Guidance for Industry entitled: "*Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*" (December 2019). That publication is available at the following link.

https://www.fda.gov/media/133660/download

The extent to which the results of Study 301, 103, and the Wave 2 and Wave 2+ results and analyses, independently or in aggregate, support or undermine the results of Study 302 will be a matter of review.

Your plan to submit a marketing application that relies on the results of Study 302 to form the primary basis of a demonstration of substantial evidence of effectiveness of aducanumab with a presentation of your stance on the supportive understanding provided by Study 301, Study 103, Wave 2, and Wave 2+ appears reasonable.

Discussion:

The sponsor opened the meeting by noting alignment with the Agency's preliminary feedback to Questions 1-3 regarding the evidence to be submitted to demonstrate the effectiveness of aducanumab. The sponsor then presented a series of slides providing an overview of the aducanumab development program with a focus on the data that are to be submitted to support the effectiveness of aducanumab. After the presentation, there were questions, answers, and comments provided by both the Agency and the sponsor. Among the issues discussed were the following:

After the sponsor presented an analysis censoring data resulting from patients that was obtained after the start of approved medications for Alzheimer's disease in Study 301 and Study 302, the Agency asked if a similar analysis had been done for Study 103 and suggested that the results of such an analysis of the effect of the 10 mg/kg dose of aducanumab in that study may also be sensitive to the same issue. The sponsor noted that such an analysis had not been performed and that the subgroup population in Study 103 was substantially smaller than those in Studies 301 and 302.

The Agency also commented on the Aβ positron emission tomographic standard uptake value ratio (SUVR) data and their relationship to the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) data as presented by the sponsor (see slide 25 of the sponsor's presentation); these were derived from Study 302. Several issues were noted by the Agency:

- These imaging data were obtained in a substudy in which the treatment groups were not directly randomized.
- There were 12% more subjects in the 71-80 year age range in the high-dose aducanumab group than in the placebo group.
- There was a 10% imbalance in ApoE4 carrier status in those completing this substudy to Week 78.
- These two factors (i.e., imbalances) may have contributed to the observed trend to a difference in efficacy from one dose level to the next on the CDR-SB, which may limit the generalizability of the Aβ data derived from positron emission tomography.
- Some of the observed patterns in subgroups also raise questions as to how predictive of changes in the CDR-SB are changes in Aβ positron emission tomography SUVR.

- For example, there was a consistently better effect of aducanumab in the ApoE4-positive subgroup than in the ApoE4-negative subgroup on the CDR-SB, but the converse was true for the effect on cerebellar SUVR.
- A similar inconsistency in aducanumab effect on the CDR-SB and SUVR was also seen in a subgroup analysis that was based on the severity of disease at baseline.

In response to these subgroup-focused comments, the sponsor noted the importance of considering differences in actual drug exposure in subgroups when evaluating the effects of aducanumab on the standard uptake value ratio and asked if the Agency's comments reflected consideration of actual drug exposure. The Agency indicated that the comments above were based upon assigned dose group.

There was also a discussion of the propensity score matched dose-response analyses displayed in Slides 27-29 of the sponsor's presentation. The Agency asked about the discrepancy between Study 301 and Study 302 in the effects seen for the middle dose group (1-7 uninterrupted doses). The sponsor posited that patients in the middle dose group had aducanumab exposures that were insufficient to consistently overcome other sources of variability in the CDR-SB assessment. Under that premise, only patients who received consistent, uninterrupted doses of 10 mg/kg (i.e., >= 8 uninterrupted doses) were able to overcome sources of variability and demonstrate a consistent effect on the CDR-SB. The Agency noted that while factors such as the proportion of rapid progressors and number of uninterrupted doses may have contributed to the difference observed between Study 301 and Study 302 in the effects of the high dose of aducanumab (10 mg/kg), they did not entirely explain that difference.

Question 4: Does the Agency agree that the aducanumab safety data from Studies 301 and 302 support an acceptable safety profile for filing?

FDA Response to Question 4:
The available data suggest that aducanumab has a safety profile that is in form acceptable to support the filing of your proposed BLA. However, the final acceptability of those data, to support both the filing of that application and its approval, will be a matter of review.

In your planned BLA submission, you should include safety evaluations for Studies 301, 302, and 103, individually, in addition to the pooled safety data that you propose to submit in that application.

Please refer to Attachment A for standard safety requests. In your BLA submission, you should include both the information and presentation requested in that document.

Discussion:
The sponsor acknowledged the Agency's response to Question 4, including the safety data requested in that response.

Question 5: During the Phase 3 studies, routine MRIs were performed to detect ARIA. Does the Agency agree that routine MRIs should be part of the labeled use of aducanumab, and that the frequency of routine MRIs can be determined by evaluation of the frequency and clinical outcomes associated with radiographically moderate to severe ARIA?

FDA Response to Question 5:
Your proposal is acceptable in form. The specifics of what will be stated in product labeling, should your application be approved, regarding the frequency and other aspects of routine magnetic resonance imaging (MRI) in patients who are administered aducanumab will be determined after review of the planned BLA.

Discussion:
The sponsor presented a summary of selected safety data for aducanumab. Those data consisted almost entirely of observed data for ARIA. The principles that are to guide the sponsor's proposal for routine MRI monitoring in patients receiving aducanumab post-approval were also outlined. See Slides 33 to 42 of the sponsor's presentation for further details.

Additional Clinical Pharmacology Comment
There is no clinical pharmacology-related information included in this meeting package other than descriptions of population pharmacokinetic-pharmacodynamic relationships, and exposure-response analyses. Therefore, we cannot comment on the adequacy of the clinical pharmacology package for your planned BLA.

The general expectations for submitting pharmacometric analyses datasets, codes, and related items can be found at:

https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/modeldata-format

Discussion:
None.

ADDITIONAL PRELIMINARY PRE-BLA COMMENTS
We note that a Pre-BLA meeting has been scheduled for July 8, 2020, to discuss this application, and that an information package for that meeting has been submitted by you on June 8, 2020. In the cover letter to that submission, you have indicated an openness to the Agency responding to the contents of that submission with written responses only. On reviewing that submission, we note that the questions contained therein are limited in scope; for that reason, we have opted to provide the answers to those questions below rather in a separate letter, and as written responses only. Thus, you may review those responses as final, rather than preliminary; however, if you wish to discuss any of these responses further during the Type C meeting scheduled for

June 17, 2020, we will address your additional questions as time permits and describe that discussion in the minutes of that Type C meeting.

Question 1: Does the Agency agree that given the low number of participants treated in the redosing study of aducanumab (Study 221AD304) and the lack of any other ongoing clinical studies, a post submission safety update is not warranted?

FDA Response to Question 1:
We do not agree that no post-submission safety update whatsoever is needed. You should provide a focused post-submission safety update that includes expected and unexpected serious adverse events, together with new reports of ARIA and follow-up information on patients reported as having ARIA in the original BLA submission who were enrolled in Study 221AD304. Please include these reports in your safety update regardless of whether they have also been submitted to IND 106230.

***Discussion*:**
None.

Question 2: Does the Agency agree with the proposal below for submission of CRFs and narratives?

FDA Response to Question 2:
Your proposal is acceptable. In addition, please see our instructions regarding narratives as well as patient profiles that are provided under the heading "*DNP Pre-NDA/Pre-BLA Meetings General Clinical Safety Requests*" in Attachment A; these are standard requests that we make for BLA and NDA submissions.

In your proposal, you state that case report forms (CRFs) and narratives will be provided for all subjects with ARIA, except for those with events of ARIA that were not serious, did not lead to study discontinuation, or were not associated with severe symptoms. Please detail what ARIA-related data you propose to provide for subjects with ARIA for whom CRFs and narratives will not be provided.

Discussion:
None.

Question 3: ARIA is the most common AE that occurs during treatment with aducanumab. ARIA typically occurs early during treatment (within the first 8 doses) and is mostly asymptomatic and transient. Biogen proposes to implement a Communication Plan REMS program that includes (b) (4) to inform and educate about the risk of ARIA and safe use of aducanumab. Does the Agency agree with this this proposal?

FDA Response to Question 3:

Your proposal for a Communication Plan Risk Evaluation and Mitigation Strategy (REMS) appears reasonable on its face. However, at this time, the Agency has insufficient information to determine whether a REMS, in any form, will be necessary to ensure that the benefits of aducanumab outweigh its risks, and if a REMS is necessary, what its required elements will be. We will determine the need for a REMS during the review of your application.

Discussion:
The sponsor outlined the rationale for including a Communication Plan REMS. The Agency recommended that the same rationale be described in the forthcoming BLA submission.

Question 4: Aducanumab is a new treatment option for a serious, life-threatening condition with no approved therapies. Does the Agency agree that aducanumab should be considered for Priority Review based on this rationale?

FDA Response to Question 4:
A request for priority review of your application will be considered at the time your application has been submitted.

Discussion:
None.

Question 5: Does the Agency agree with Biogen's proposed SDSP?

FDA Response to Question 5:
Your proposed Study Data Standardization Plan is acceptable.

Discussion:
None.

Question 6: Does the Agency anticipate convening an Advisory Committee meeting for this application?

FDA Response to Question 6:
A final determination regarding the need for an Advisory Committee meeting will be determined during review of your complete marketing application. At this time, it is reasonable to plan for the occurrence of an Advisory Committee meeting during the conduct of the review of your application.

Discussion:
None.

Question 7: Based on the contemporary understanding of Alzheimer's disease as a continuum, Biogen is considering the following options to describe the patient population in the draft USPI:

- Patients with Alzheimer's disease
- [redacted] (b) (4)

Can the Agency please advise which patient population would be most appropriate?

FDA Response to Question 7:
The language to be used to describe such patients in the Prescribing Information for aducanumab, should your application be approved, will be determined during the review of your planned BLA. With that said, we recognize that you ask this question with regard to structuring the draft labeling required for inclusion in your application, [redacted] (b) (4) Recognizing, and reiterating, that commenting definitively on any expectation we may have about specific language to be included in the Prescribing Information for aducanumab, should your application be approved, is premature, we can state that a reasonable approach to take for your draft labeling is to structure your labeling proposal based on an indication statement for the treatment of patients with Alzheimer's disease.

Discussion:
The Agency indicated that, in describing the stages of Alzheimer's disease in the relevant sections of any future Prescribing Information for aducanumab, should such description be needed (e.g., it is possible that Section 14 might include such a description), terminology similar to that contained in the draft Guidance for Industry entitled "*Early Alzheimer's Disease: Developing Drugs for Treatment*" (February 2018) would be likely to be used.

Additional Comments Regarding Safety Data
The following additional ARIA-related safety data would be useful in the review of your BLA.

- Kaplan-Meier survival curves for the following variables: all ARIA-E and first ARIA-E for all subjects and for subject categories as determined by aducanumab dose and ApoE4 carrier status; isolated ARIA-H and ARIA-H occurring together with ARIA-E for all subjects and for subject categories as determined by aducanumab dose and ApoE4 carrier status.

- Analyses showing the relationship, in any, between specific adverse events such as falls and headaches with the presence of ARIA, especially ARIA-E.

The above data may be submitted for pooled study groups as well as the individual studies 301, 302, and 103.

Discussion:
The Agency indicated to the sponsor that more analyses of ARIA-related safety data, additional to those described immediately above, were to be requested by the Agency, for inclusion in the planned BLA, and would be sent independently to the sponsor shortly after the meeting.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

guidance on pediatric product development, please refer to FDA.gov.[3]

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

- In addition, we note that a chemistry pre-submission meeting scheduled for March 25, 2020. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

reproductive potential.

- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[6]

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER*

[6] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Submissions, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[7]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

[7] https://www.fda.gov/media/85061/download

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

Attachment A:

DNP Pre-NDA/Pre-BLA Meetings
General Clinical Safety Requests

General Submission Contents:

1. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
2. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
3. Submit an annotated version of the pre-NDA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.
4. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
5. Include active hyperlinks from the lists of references to the referenced article.
6. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application
7. Provide an assessment of safety as per the FDA Guidance for Industry: Premarketing Risk Assessment
8. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.
9. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:
   a. Title of the table or figure in the application
   b. A hyperlink to the location of the table or figure with page number
   c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)
10. Format the tables of the ISS according to examples in FDA's Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event,

MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.

3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. Ensure that all adverse events are presented, and not only events deemed "drug-related."
5. Provide a table of treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
6. Provide a table which summarizes the outcomes of all pregnancies including the reasons for termination if this occurred. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, all discontinuations, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request.
2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the case report form and/or narrative.
3. Provide reports for any autopsies conducted during any of the studies.
4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law lab criteria.
5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them "CRFs", e.g., Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
6. Provide both narratives and CRFs for all discontinuations (including Lost to follow-up, Other, Physician/investigator decision, Patient decision, Withdrew consent). Provide a tabular listing of all subjects with discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for discontinuation; for reasons including Lost to follow-up, Other, Physician/investigator decision, withdrew consent, and Patient decision, provide more specific information regarding the discontinuation.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
   - Patient age and gender
   - Adverse event onset and stop dates (presented as relative Study Day number)
   - Signs and symptoms related to the adverse event being discussed
   - An assessment of the relationship of exposure duration to the development of the adverse event
   - Pertinent medical history
   - Concomitant medications with start dates relative to the adverse event
   - Pertinent physical exam findings

- Any abnormal vital sign measurements
- Pertinent test results (e.g., lab data, ECG data, biopsy data, autopsy results)
- Discussion of the diagnosis as supported by available clinical data
- For events without a definitive diagnosis, a list of the differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests: SI Units
2. Provide the normal reference ranges for every laboratory value.
3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs data and ECG data.
4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.
5. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:
   - Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
   - Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
   - Pulse Rate: <60 bpm, >100 bpm
   - Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
   - Temperature: >38.0 °C, <36.0 °C
   - Respiratory rate: <12 breaths/min, > 20 breaths/min
6. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

1. Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:
   - Age
   - Sex
   - Dates of screening, randomization and starting therapy
   - Whether the patient completed or did not complete the study, with dates and reason for withdrawal
   - Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
   - Prior medications and concomitant medications with dates of start and end
   - Vital signs and laboratories, sorted by date, with reference ranges *
   - Full reports for radiologic studies, ECG, MRI, pathology results, and special studies with dates and reference ranges *

- Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)

* Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.

For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted to IND 106533.
Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

4.0 ATTACHMENTS AND HANDOUTS

Attached are the documents presented by Biogen during the June 17, 2020, Type C Meeting.

48 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS
07/02/2020 04:20:17 PM

IND 106230

MEETING PRELIMINARY COMMENTS

Biogen, Inc.
Attention: Priya Singhal, MD, MPH
Senior Vice President, Global Safety and Regulatory Sciences
225 Binney St.
Cambridge, MA 02142

Dear Dr. Singhal:[1]

Please refer to your Investigational New Drug Application (IND) file for aducanumab.

We also refer to your correspondence, dated and received February 7, 2020, requesting a meeting to discuss the development program for aducanumab.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, contact me by email at emilios.papanastasiou@fda.hhs.gov or by phone at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

E. Andrew Papanastasiou, MS, PharmD
Senior Regulatory Project Manager
Neurology 1 Group
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: June 17, 2020, from 11:00 AM to 1:00 PM
Meeting Location: FDA White Oak Building 22 Room 1417

Application Number: IND 106230
Product Name: aducanumab (BIIB037, anti-Aβ monoclonal antibody)
Indication: Alzheimer's disease
Sponsor Name: Biogen, Inc.
Regulatory Pathway: 351(a)

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 17, 2020, from 11:00 AM to 1:00 PM at the FDA White Oak Campus between Biogen, Inc. and the Division of Neurology 1. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

The overall purpose of this Type C meeting is to discuss the efficacy and safety data that are currently available for aducanumab (BIIB037) in the context of a planned Biologics License Application (BLA) for that compound. Aducanumab is a humanized

monoclonal antibody to β-amyloid. The currently-proposed indication for aducanumab is [redacted (b) (4)].

Two Phase 3 studies, 221AD301 (Study 301) and 221AD302 (Study 302), that were identical in design have been conducted with aducanumab. The primary objective of each study was to evaluate the efficacy of monthly doses of aducanumab in the treatment of patients with early Alzheimer's disease; each was a randomized, double-blind, placebo-controlled, parallel-arm study with an initial placebo-controlled period of 78 weeks to be followed by a long-term extension up to 5 years. The primary efficacy parameter was the change from baseline to Week 78 in Clinical Dementia Rating Scale – Sum of Boxes score. Secondary efficacy parameters included the change from baseline to Week 78 in Mini-Mental Status Examination, 13-item Alzheimer's Disease Assessment Scale – Cognitive, and Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale scores. Biomarker-based outcome measures were to include: amyloid positron emission tomographic signal; several measures derived from volumetric brain magnetic resonance imaging; and others. Safety measures were to include adverse events, vital signs, electrocardiograms, safety laboratory tests, anti-aducanumab antibody titers, brain MRI, and a suicidality assessment.

Studies 301 and 302 were discontinued on March 21, 2019, after a prespecified interim futility analysis indicated that the prespecified criteria for futility were met and that those studies were unlikely to meet their primary endpoint on completion. The interim analysis of futility included all data available as of December 26, 2018, for all study patients randomized at least 78 weeks prior to that date. The results of that analysis led to both studies being discontinued on March 21, 2019.

Subsequent efficacy analyses, based on data available through March 20, 2019, had yielded results that questioned the earlier assessment of futility. Those subsequent efficacy analyses and the next steps to be taken were discussed at a face-to-face Type C meeting between the Agency and sponsor on June 14, 2019. At that meeting, it was recommended to the sponsor that further analyses of the efficacy data for Studies 301 and 302 be conducted under a collaborative workstream between the Agency and sponsor.

After the Type C meeting on June 14, 2019, additional analyses of the results of Studies 301 and 302 were conducted jointly by the Agency and sponsor under a collaborative workstream. Those analyses have been conducted in two waves first agreed upon at a meeting held on July 2, 2019:

- Wave 1: To determine whether early termination of Studies 301 and 302 may have impacted the interpretation of efficacy data for those studies and to determine which dataset was appropriate to use for the additional analyses to be conducted in Wave 2.

- Wave 2: To understand the consistency of and differences in the efficacy results of Studies 301 and 302.

After the Waves 1 and 2 analyses were completed, they were further discussed between the Agency and sponsor at a face-to-face Type C meeting held on October 21, 2019. Please see the minutes of that meeting for full details of what was discussed at that time.

Subsequent to that meeting, and in extension of the Wave 1 and 2 analyses, the collaborative workstream then sought to address additional questions generated during the Wave 2 analyses; that additional effort was termed "Wave 2+," the aims of which were as follows:

1. To use propensity score matching to supplement previous work assessing whether subgroups in Study 301 had outcomes similar to the overall results in Study 302. Wave 2 utilized unmatched placebo groups and placebo groups matched on apolipoprotein E ε4 (ApoE ε4) carrier status and enrollment timing.

2. To further characterize the dose-exposure-response relationship.

3. To refine and extend pharmacokinetic-pharmacodynamic models through use of the additional data available in the final database.

4. To characterize associations between changes in amyloid beta positron emission tomography standardized uptake value ratio (Aβ PET SUVR) and clinical outcomes.

The additional analyses subsumed under Wave 2+ used data not only from Studies 301 and 302, but also from a Phase 1b randomized, double-blind, placebo-controlled study 221AD103 (Study 103). The results of those analyses and their implications were discussed at a further Type C meeting held between the Agency and sponsor on February 27, 2020. Please see the minutes of that meeting for further details.

Subsequent to the meeting on February 27, 2020, there have been further interactions between the Agency and sponsor as part of the aforementioned collaborative workstream.

The results of the analyses described above, other efficacy-related analyses, and analyses of safety data for aducanumab have been summarized in full in the meeting package submitted by the sponsor. As stated in this meeting package, the sponsor "*seeks to discuss the primary basis for effectiveness for the intended BLA submission and the safety profile of aducanumab, especially focusing on amyloid-related imaging abnormalities (ARIA), the adverse event (AE) of special interest*."

On June 8, 2020, subsequent to the submission of this Type C meeting package, the sponsor submitted a Pre-BLA meeting package. While a formal Pre-BLA meeting between the Agency and sponsor has been scheduled for July 8, 2020, the sponsor has also stated in the cover letter to that submission an openness to the Agency responding to the contents of that submission with written responses only. Topics covered in the Pre-BLA meeting package regarding which the sponsor has sought Agency advice include the following: the need for a post-BLA safety update; a proposal for the submission of patient case report forms and narratives; a proposal for a Communication Risk Evaluation and Mitigation Strategy (REMS) program addressing ARIA; the proposed Study Data Standardization Plan (SDSP); the terms that might be used to describe patients enrolled in the aducanumab clinical trials in the US Prescribing Information; whether the planned BLA may qualify for a priority review; and whether that application may need discussion at a meeting of the Peripheral and Central Nervous System Drug Advisory Committee. For the reasons noted below (see ADDITIONAL PRE-BLA COMMENTS), the questions in that meeting package are also addressed in this letter.

2.0 DISCUSSION

Question 1: Does the Agency agree that Study 302 is a positive trial in the study population on its prespecified primary endpoint with support from secondary and biomarker endpoints in the context of Wave 1, and will provide the primary evidence in support of the effectiveness of aducanumab?

FDA Response to Question 1:
The Wave 1 analysis established that early termination of Study 302 and Study 301 did not compromise the interpretability of the results of those studies. Therefore, the results of Study 302 appear reliable and on face represent a positive trial with support from secondary and biomarker endpoints. Considering that the Wave 1 analysis also established Study 301 as a negative study, it follows that Study 302 would serve as the primary source of evidence in support of the effectiveness of aducanumab in a marketing application.

Question 2: Does the Agency agree that Wave 2 and Wave 2+ provide additional data from Study 301 that further supports the understanding of the effectiveness of aducanumab as demonstrated in Study 302?

FDA Response to Question 2:
As noted in the minutes of the Type C meeting held between the Agency and you on February 27, 2020, the Wave 2 and Wave 2+ analyses may help provide an overall understanding of the efficacy data for aducanumab and will be considered in terms of their ability to support or undermine the independent results of Study 302. The analyses do not, however, appear capable of providing independent evidence of effectiveness.

The extent to which those analyses support or undermine the results of Study 302 will be a matter of review.

Question 3: In light of Question 1 and Question 2, does the Agency agree that the results of Study 302 form the basis of a demonstration of substantial evidence of effectiveness of aducanumab in the context of the submission with supportive understanding provided by Study 301, Study 103, Wave 2 and Wave 2+?

FDA Response to Question 3:
Please see our responses to Questions 1 and 2. The circumstances under which a single adequate and well-controlled study (Study 302) can be used as the sole basis for demonstrating the efficacy of a drug or biologic are discussed in the draft Guidance for Industry entitled: "*Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*" (December 2019). That publication is available at the following link.

https://www.fda.gov/media/133660/download

The extent to which the results of Study 301, 103, and the Wave 2 and Wave 2+ results and analyses, independently or in aggregate, support or undermine the results of Study 302 will be a matter of review.

Your plan to submit a marketing application that relies on the results of Study 302 to form the primary basis of a demonstration of substantial evidence of effectiveness of aducanumab with a presentation of your stance on the supportive understanding provided by Study 301, Study 103, Wave 2, and Wave 2+ appears reasonable.

Question 4: Does the Agency agree that the aducanumab safety data from Studies 301 and 302 support an acceptable safety profile for filing?

FDA Response to Question 4:
The available data suggest that aducanumab has a safety profile that is in form acceptable to support the filing of your proposed BLA. However, the final acceptability of those data, to support both the filing of that application and its approval, will be a matter of review.

In your planned BLA submission, you should include safety evaluations for Studies 301, 302, and 103, individually, in addition to the pooled safety data that you propose to submit in that application.

Please refer to Attachment A for standard safety requests. In your BLA submission, you should include both the information and presentation requested in that document.

Question 5: During the Phase 3 studies, routine MRIs were performed to detect ARIA. Does the Agency agree that routine MRIs should be part of the labeled use of

aducanumab, and that the frequency of routine MRIs can be determined by evaluation of the frequency and clinical outcomes associated with radiographically moderate to severe ARIA?

FDA Response to Question 5:
Your proposal is acceptable in form. The specifics of what will be stated in product labeling, should your application be approved, regarding the frequency and other aspects of routine magnetic resonance imaging (MRI) in patients who are administered aducanumab will be determined after review of the planned BLA.

Additional Clinical Pharmacology Comment
There is no clinical pharmacology-related information included in this meeting package other than descriptions of population pharmacokinetic-pharmacodynamic relationships, and exposure-response analyses. Therefore, we cannot comment on the adequacy of the clinical pharmacology package for your planned BLA.

The general expectations for submitting pharmacometric analyses datasets, codes, and related items can be found at:

https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/modeldata-format

ADDITIONAL PRE-BLA COMMENTS
We note that a Pre-BLA meeting has been scheduled for July 8, 2020, to discuss this application, and that an information package for that meeting has been submitted by you on June 8, 2020. In the cover letter to that submission, you have indicated an openness to the Agency responding to the contents of that submission with written responses only. On reviewing that submission, we note that the questions contained therein are limited in scope; for that reason, we have opted to provide the answers to those questions below rather in a separate letter, and as written responses only. Thus you may review those responses as final, rather than preliminary; however, if you wish to discuss any of these responses further during the Type C meeting scheduled for June 17, 2020, we will address your additional questions as time permits and describe that discussion in the minutes of that Type C meeting.

Question 1: Does the Agency agree that given the low number of participants treated in the redosing study of aducanumab (Study 221AD304) and the lack of any other ongoing clinical studies, a post submission safety update is not warranted?

FDA Response to Question 1:
We do not agree that no post-submission safety update whatsoever is needed. You should provide a focused post-submission safety update that includes expected and unexpected serious adverse events, together with new reports of ARIA and follow-up

information on patients reported as having ARIA in the original BLA submission who were enrolled in Study 221AD304. Please include these reports in your safety update regardless of whether they have also been submitted to IND 106230.

Question 2: Does the Agency agree with the proposal below for submission of CRFs and narratives?

FDA Response to Question 2:
Your proposal is acceptable. In addition, please see our instructions regarding narratives as well as patient profiles that are provided under the heading "*DNP Pre-NDA/Pre-BLA Meetings General Clinical Safety Requests*" in Attachment A; these are standard requests that we make for BLA and NDA submissions.

In your proposal, you state that case report forms (CRFs) and narratives will be provided for all subjects with ARIA, except for those with events of ARIA that were not serious, did not lead to study discontinuation, or were not associated with severe symptoms. Please detail what ARIA-related data you propose to provide for subjects with ARIA for whom CRFs and narratives will not be provided.

Question 3: ARIA is the most common AE that occurs during treatment with aducanumab. ARIA typically occurs early during treatment (within the first 8 doses) and is mostly asymptomatic and transient. Biogen proposes to implement a Communication Plan REMS program that includes (b) (4) to inform and educate about the risk of ARIA and safe use of aducanumab. Does the Agency agree with this this proposal?

FDA Response to Question 3:
Your proposal for a Communication Plan Risk Evaluation and Mitigation Strategy (REMS) appears reasonable on its face. However, at this time, the Agency has insufficient information to determine whether a REMS, in any form, will be necessary to ensure that the benefits of aducanumab outweigh its risks, and if a REMS is necessary, what its required elements will be. We will determine the need for a REMS during the review of your application.

Question 4*:* Aducanumab is a new treatment option for a serious, life-threatening condition with no approved therapies. Does the Agency agree that aducanumab should be considered for Priority Review based on this rationale?

FDA Response to Question 4:
A request for priority review of your application will be considered at the time your application has been submitted.

Question 5: Does the Agency agree with Biogen's proposed SDSP?

FDA Response to Question 5:
Your proposed Study Data Standardization Plan is acceptable.

Question 6: Does the Agency anticipate convening an Advisory Committee meeting for this application?

FDA Response to Question 6:
A final determination regarding the need for an Advisory Committee meeting will be determined during review of your complete marketing application. At this time, it is reasonable to plan for the occurrence of an Advisory Committee meeting during the conduct of the review of your application.

Question 7: Based on the contemporary understanding of Alzheimer's disease as a continuum, Biogen is considering the following options to describe the patient population in the draft USPI:

- Patients with Alzheimer's disease
- (b) (4)

Can the Agency please advise which patient population would be most appropriate?

FDA Response to Question 7:
The language to be used to describe such patients in the Prescribing Information for aducanumab, should your application be approved, will be determined during the review of your planned BLA. With that said, we recognize that you ask this question with regard to structuring the draft labeling required for inclusion in your application, (b) (4) Recognizing, and reiterating, that commenting definitively on any expectation we may have about specific language to be included in the Prescribing Information for aducanumab, should your application be approved, is premature, we can state that a reasonable approach to take for your draft labeling is to structure your labeling proposal based on an indication statement for the treatment of patients with Alzheimer's disease.

Additional Comments Regarding Safety Data

The following additional ARIA-related safety data would be useful in the review of your BLA.

- Kaplan-Meier survival curves for the following variables: all ARIA-E and first ARIA-E for all subjects and for subject categories as determined by aducanumab dose and ApoE4 carrier status; isolated ARIA-H and ARIA-H occurring together with ARIA-E for all subjects and for subject categories as determined by aducanumab dose and ApoE4 carrier status.

- Analyses showing the relationship, in any, between specific adverse events such as falls and headaches with the presence of ARIA, especially ARIA-E.

The above data may be submitted for pooled study groups as well as the individual studies 301, 302, and 103.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended*

Pediatric Study Plans.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

SECURE EMAIL COMMUNICATIONS

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[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

Attachment A.

DNP Pre-NDA/Pre-BLA Meetings
General Clinical Safety Requests

General Submission Contents:

1. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
2. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
3. Submit an annotated version of the pre-NDA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.
4. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
5. Include active hyperlinks from the lists of references to the referenced article.
6. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application
7. Provide an assessment of safety as per the FDA Guidance for Industry: Premarketing Risk Assessment
8. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.
9. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:
   a. Title of the table or figure in the application
   b. A hyperlink to the location of the table or figure with page number
   c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)
10. Format the tables of the ISS according to examples in FDA's Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event,

MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.

3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. Ensure that all adverse events are presented, and not only events deemed "drug-related."
5. Provide a table of treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
6. Provide a table which summarizes the outcomes of all pregnancies including the reasons for termination if this occurred. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, all discontinuations, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request.
2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the case report form and/or narrative.
3. Provide reports for any autopsies conducted during any of the studies.
4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law lab criteria.
5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them "CRFs", e.g., Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
6. Provide both narratives and CRFs for all discontinuations (including Lost to follow-up, Other, Physician/investigator decision, Patient decision, Withdrew consent). Provide a tabular listing of all subjects with discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for discontinuation; for reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
   - Patient age and gender
   - Adverse event onset and stop dates (presented as relative Study Day number)
   - Signs and symptoms related to the adverse event being discussed
   - An assessment of the relationship of exposure duration to the development of the adverse event
   - Pertinent medical history
   - Concomitant medications with start dates relative to the adverse event
   - Pertinent physical exam findings

- Any abnormal vital sign measurements
- Pertinent test results (e.g., lab data, ECG data, biopsy data, autopsy results)
- Discussion of the diagnosis as supported by available clinical data
- For events without a definitive diagnosis, a list of the differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests: SI Units
2. Provide the normal reference ranges for every laboratory value.
3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs data and ECG data.
4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.
5. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:
   - Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
   - Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
   - Pulse Rate: <60 bpm, >100 bpm
   - Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
   - Temperature: >38.0 °C, <36.0 °C
   - Respiratory rate: <12 breaths/min, > 20 breaths/min
6. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

1. Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:
   - Age
   - Sex
   - Dates of screening, randomization and starting therapy
   - Whether the patient completed or did not complete the study, with dates and reason for withdrawal
   - Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
   - Prior medications and concomitant medications with dates of start and end
   - Vital signs and laboratories, sorted by date, with reference ranges *
   - Full reports for radiologic studies, ECG, MRI, pathology results, and special studies with dates and reference ranges *

- Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)

* Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.

For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted to IND 106533.
Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EMILIOS A PAPANASTASIOU
06/12/2020 05:47:50 PM

IND 106230

MEETING MINUTES

Biogen, Inc.
Attention: Priya Singhal, MD, MPH
Senior Vice President, Global Safety and Regulatory Sciences
225 Binney St.
Cambridge, MA 02142

Dear Dr. Singhal:[1]

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for aducanumab.

We also refer to the meeting between representatives of your firm and the FDA on February 27, 2020. The purpose of the meeting was to discuss the development plan for aducanumab.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact E. Andrew Papanastasiou, Regulatory Project Manager, by email at emilios.papanastasiou@fda.hhs.gov or by phone at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Acting Director
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: February 27, 2020, from 1:00 PM to 2:30 PM

Meeting Location: FDA White Oak Building 22 Room 1417

Application Number: IND 106230
Product Name: aducanumab (BIIB037)

Sponsor: Biogen, Inc.

FDA ATTENDEES

Billy Dunn, MD - Director, Office of Neuroscience
Eric Bastings, MD - Acting Director, Division of Neurology 1 (DN1)
Nicholas Kozauer, MD - Acting Deputy Director, DN2
Ranjit Mani, MD - Clinical Team Leader, DN1
Brian Trummer, MD, PhD - Clinical Reviewer, DN1
Kevin Krudys, PhD - Senior Clinical Analyst, DN1
Natalie Branagan, MD - Safety Reviewer
Kun Jin, PhD - Biostatistics Team Leader
Tristan Massie, PhD - Statistical Reviewer
Sue Jane Wang, PhD - Associate Office Director, Biometrics I
Hsien Ming (Jim) Hung, PhD - Director, Division of Biometrics I
Daniel Ngembus, PharmD - Regulatory Project Manger
E. Andrew Papanastasiou, MS, PharmD - Senior Regulatory Project Manager

SPONSOR ATTENDEES

Samantha Budd Haeberlein - VP, Clinical Development
Christian von Hehn - Medical Director, Clinical Development
Barbara Kolb - Executive Director, US Regulatory Sciences
Angela Neufeld - Director, Global Regulatory Sciences
Kiley Mitrano - Associate Director, US Regulatory Sciences
Brianne FitzGerald - Manager, US Regulatory Sciences
LeAnne Skordos - Director, Clinical Program Leadership
Ying Tian - Director, Biostatistics
Ying Zhu - Distinguished Biostatistician
Craig Mallinckrodt - Senior Director, Biostatistics
Shuang Wu - Associate Director, Biostatistics
Tianle Chen - Principal Biostatistician
Jie Li - Associate Director, Biostatistics

Raj Rajagovindan - Associate Director, Development Imaging
Ivan Nestorov - Senior Director, Pharmacometrics
Kumar Kandadi Muralidharan - Director, Pharmacometrics
Martin Rabe (Eisai) - Vice President, Global Regulatory Strategy
Michael Irizarry (Eisai) - Vice President, Clinical Research

1.0 BACKGROUND

This meeting package discusses further analyses mainly of two Phase 3 clinical trials of aducanumab (BIIB037) that were terminated early in 2019, based on the results of an interim analysis of futility.

BIIB037 is a humanized monoclonal antibody to β-amyloid under development for (b) (4) .

The two Phase 3 studies, 221AD301 (Study 301) and 221AD302 (Study 302), were identical in design. The primary objective of each study was to evaluate the efficacy of monthly doses of aducanumab in the treatment of patients with early Alzheimer's disease; each was a randomized, double-blind, placebo-controlled, parallel-arm study with an initial placebo-controlled period of 78 weeks to be followed by a long-term extension up to 5 years. The primary efficacy parameter was the change from baseline to Week 78 in Clinical Dementia Rating Scale – Sum of Boxes score. Secondary efficacy parameters included the change from baseline to Week 78 in Mini-Mental Status Examination, 13-item Alzheimer's Disease Assessment Scale – Cognitive, and Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale scores. Biomarker-based outcome measures were to include: amyloid positron emission tomographic signal; several measures derived from volumetric brain magnetic resonance imaging; and others. Safety measures were to include adverse events, vital signs, electrocardiograms, safety laboratory tests, anti-aducanumab antibody titers, brain MRI, and a suicidality assessment.

Studies 301 and 302 were discontinued on March 21, 2019, after a prespecified interim futility analysis indicated that the prespecified criteria for futility were met and that those studies were unlikely to meet their primary endpoint on completion. The interim analysis of futility included all data available as of December 26, 2018, for all study patients randomized at least 78 weeks prior to that date. The results of that analysis led to both studies being discontinued on March 21, 2019.

Subsequent efficacy analyses, based on data available through March 20, 2019, had yielded results that questioned the earlier assessment of futility. Those subsequent efficacy analyses and the next steps to be taken were discussed at a face-to-face Type C meeting between the Agency and sponsor on June 14, 2019. At that meeting, it was recommended to the sponsor that further analyses of the efficacy data for Studies 301 and 302 be conducted under a collaborative workstream between the Agency and

sponsor. It was also conveyed to the sponsor that there were five options (or conclusions) that might follow the additional analyses to be conducted under that collaborative workstream.

1. Adequate evidence exists that aducanumab is ineffective.

2. The results of Study 302 establish the effectiveness of aducanumab, with Study 301 providing supportive data, so that a standard (full approval) for aducanumab could be considered.

3. The results of Study 302 establish the effectiveness of aducanumab, with Study 301 not providing supportive data, but with the results of Study 301 being sufficiently well understood to be dismissible; a standard (full approval) for aducanumab could again be considered.

4. Accelerated approval of aducanumab may be considered based on a persuasive effect in reducing brain amyloid accompanied by a reasonable likelihood of clinical benefit based on the available clinical results.

5. An additional clinical study of aducanumab should be conducted based on a suggestion of clinical effectiveness seen thus far in the clinical development program, that after further exploration and consideration, proves inadequate to independently establish effectiveness.

After the Type C meeting on June 14, 2019, additional analyses of the results of Studies 301 and 302 were conducted jointly by the Agency and sponsor under a collaborative workstream. Those analyses have been conducted in two waves first agreed upon at a meeting held on July 2, 2019:

- Wave 1: To determine whether early termination of Studies 301 and 302 may have impacted the interpretation of efficacy data for those studies and to determine which dataset was appropriate to use for the additional analyses to be conducted in Wave 2.

- Wave 2: To understand the consistency of and differences in the efficacy results of Studies 301 and 302.

Waves 1 and 2 were to be followed by Wave 3 which was to consider which of the five options presented to the sponsor at the Type C meeting held on June 14, 2019, were supported by the outcomes of Waves 1 and 2.

After the Waves 1 and 2 analyses were completed, they were further discussed between the Agency and sponsor at a face-to-face Type C meeting held on October 21, 2019. Please see the minutes of that meeting for full details of what was discussed at that time.

Subsequent to that meeting, and in extension of the Wave 1 and 2 analyses, the collaborative workstream then sought to address additional questions generated during the Wave 2 analyses; that additional effort was termed “Wave 2+,” the aims of which were as follows:

1. To use propensity score matching to supplement previous work assessing whether subgroups in Study 301 had outcomes similar to the overall results in Study 302. Wave 2 utilized unmatched placebo groups and placebo groups matched on apolipoprotein E ε4 (ApoE ε4) carrier status and enrollment timing.

2. To further characterize the dose-exposure-response relationship.

3. To refine and extend pharmacokinetic-pharmacodynamic models through use of the additional data available in the final database.

4. To characterize associations between changes in amyloid beta positron emission tomography standardized uptake value ratio (Aβ PET SUVR) and clinical outcomes.

The additional analyses subsumed under Wave 2+ are now complete; they used data not only from Studies 301 and 302, but also from Phase 1b Study 221AD103 (Study 103). The results of those analyses are summarized in the current meeting package

The objective of the current meeting is to discuss the results of the additional analyses generated by the collaborative workstream under Wave 2+ and their implications for the further development of aducanumab for the indications that the sponsor is currently seeking.

FDA sent Preliminary Comments to Biogen on February 21, 2020.

2.0 DISCUSSION

Question 1: Based on the results and the joint conclusions from the additional ‘Wave 2+’ analyses generated under the Collaborative Workstream, does the Agency agree that the ‘Wave 2+’ analyses address the questions that remained following the October 21, 2019 Type C meeting on dose / exposure-response relationship?

FDA Response to Question 1:
The additional analyses presented in this meeting package address the questions that remained following the October 21, 2019, Type C meeting and provide additional insight regarding the relationship between aducanumab dose/exposure and response in Study 301 and Study 302. Further consideration of the results of these analyses is necessarily a matter of detailed review.

We look forward to discussing the results of these additional analyses with you at the upcoming meeting.

Meeting Discussion:

The meeting began with the sponsor presenting a set of slides that summarized the analyses conducted under the collaborative workstream. These slides were intended to supplement the contents of the meeting package, and are attached to these meeting minutes. During that presentation, there were clarifying questions, answers, and comments provided by both the Agency and the sponsor.

Among the salient items discussed at the meeting were the following.

The sponsor explained that the analyses presented as part of Wave 2+ were performed using the "final" study dataset, an updated version of the "April" dataset used for the Wave 2 analyses and discussed at the Type C face-to-face meeting held on October 21, 2019. The populations included in each of these two datasets were summarized in the meeting package. Differences in results between these two datasets are expected to be minimal. The sponsor further stated that the Wave 2 analyses were to be updated using the "final" dataset and the results then shared with the Agency.

The histogram in Slide 10 of the sponsor's presentation showing the change from baseline to Week 78 in the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) score for Studies 301 and 302, and the basis for the apparently non-normal distribution of scores in that histogram, were then discussed.

The sponsor then presented the results of analyses conducted using the population exposure-CDR-SB response model using data from Studies 301 and 302. The Agency recommended that data from Study 103 be used for external validation of that model, a recommendation to which the sponsor agreed. The sponsor also asserted that the results of those analyses suggested that no discernible pharmacological differences on the rate of progression could be detected. In response, the Agency noted that as part of the modeling, it was important to reconcile that observation with the differences in clinical outcomes between Study 301 and Study 302 that have also been noted.

Next, the use of propensity score matching to determine whether subgroups enrolled in Study 301 had outcomes similar to the overall results of Study 302 was discussed. The Agency observed that the different dose-attained subgroups had inconsistent placebo effects, even after propensity score matching, limiting the ability to infer whether a dose response was present; to more fully inform this issue, the different dose groups could be matched with each other. The sponsor noted that the aducanumab treatment subgroups were nested and thus the propensity score analysis is not well-suited to show dose-response relationships. The sponsor also

commented on the fluctuating placebo means across subgroups and concluded that this fluctuation potentially accounts for some of the inconsistent drug/placebo differences observed. Further, the Agency noted that a post hoc propensity score matching-based comparison does not provide the same evidence that a truly randomized comparison might.

The Agency also expressed a concern that the apparent effect of an increase in dose of aducanumab in Study 302 may be confounded by a change in enrollment in certain countries. Examples of such an effect were provided. The Agency agreed to follow up with more details as part of the ongoing collaborative workstream.

Finally, the Agency noted that none of the analyses discussed at the meeting should be viewed in isolation and that none of the analyses are intended to provide independent substantiation of effectiveness. However, on the presumption that the results of Study 302 were accurate, it might be possible to analyze data from Study 301 with specific hypotheses under consideration, and determine whether patients in both studies had a qualitatively similar response. In the Agency's view, the analyses presented at the meeting, in combination with other previous and potentially yet to be conducted analyses, may help provide an understanding of the overall data for aducanumab and be considered in terms of their ability to support or undermine the independent results of Study 302.

The details of the next steps to be taken regarding aducanumab were discussed. These steps are as listed in Slide 32 of the sponsor's presentation at the meeting.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting

documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

4.0 ATTACHMENTS AND HANDOUTS

Attached is the handout provided by Biogen at the February 27, 2020, meeting.

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS
03/27/2020 03:59:50 PM

IND 106230

MEETING MINUTES

Biogen, Inc.
Attention: Angela M. Neufeld, MS
Associate Director, Global Regulatory Sciences
225 Binney St.
Cambridge, MA 02142

Dear Ms. Neufeld:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for aducanumab.

We also refer to the meeting between representatives of your firm and the FDA on October 21, 2019. The purpose of the meeting was to discuss data and analyses from the two recently terminated Phase 3 clinical trials of aducanumab.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact E. Andrew Papanastasiou, Regulatory Project Manager, by email at emilios.papanastasiou@fda.hhs.gov or by phone at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director (acting)
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: October 21, from 2:00 PM to 2:00 PM
Meeting Location: FDA White Oak Building 22 Room 1417

Application Number: IND 106230
Product Name: Aducanumab (BIIB037)

Indication: Alzheimer's Disease
Sponsor Name: Biogen, Inc.

FDA ATTENDEES

Billy Dunn, MD	Acting Deputy Director, ODE1
Eric Bastings, MD	Acting Director, DNP
Nicholas Kozauer, MD	Acting Deputy Director, DNP
Ranjit Mani, MD	Clinical Reviewer, DNP
Kevin Krudys PhD	Senior Clinical Analyst, DNP
Kun Jin, PhD	Biostatistics Team Leader
Tristan Massie, PhD	Statistical Reviewer
Hsien Ming (Jim) Hung, PhD	Director, Division of Biometrics I
Alina Salvatore,	Regulatory Project Manager, DNP
Viveca Livezey, MD	Clinical Reviewer, DNP
Jonathan Pomeraniec, MD	Neurology Fellow, NIH
E. Andrew Papanastasiou MS, PharmD	Regulatory Project Manager, DNP

SPONSOR ATTENDEES

Alfred Sandrock, MD, PhD	Executive Vice President, Chief Medical Officer
Samantha Budd Haeberlein, PhD	VP, Clinical Development
Christian von Hehn, MD, PhD	Medical Director, Clinical Development
Carmen Castrillo-Viguera, MD	Medical Director, Clinical Development
Spyros Chalkias, MD	Medical Director, Drug Safety
Angela Neufeld, MS	Director, Global Regulatory Sciences

Helen Lockett	Director, EU Regulatory Sciences
Ying Zhu, PhD	Distinguished Biostatistician
Ying Tian, PhD	Director, Biostatistics
Tianle Chen, PhD	Principle Biostatistician
Craig Mallinckrodt, PhD	Senior Director, Biostatistics
Shuang Wu, PhD	Associate Director, Biostatistics
Xiaopeng Miao, PhD	Associate Director, Biostatistics
Laura Nisenbaum, PhD	Senior Director, Diagnostic Pathways
Raj Rajagovindan, PhD	Associate Director, Development Imaging
Ivan Nestorov, PhD	Senior Director, Pharmacometrics
Kumar Kandadi Muralidharan, MS	Associate Director, Pharmacometrics
LeAnne Skordos, PharmD	Director, Clinical Program Leadership
Liz Miller, MS	Associate Director, Medical Writing
Martin Rabe, MSc	Vice President, Global Regulatory Strategy, Eisai
Michael Irizarry, MD	Vice President, Clinical Research, Eisai

1.0 BACKGROUND

This meeting package discusses further analyses of two Phase 3 clinical trials of aducanumab (BIIB037) that were terminated early in 2019, based on the results of an interim analysis of futility.

BIIB037 is a humanized monoclonal antibody to β-amyloid under development for the treatment of early Alzheimer's disease.

The two Phase 3 studies, 221AD301 (Study 301) and 221AD302 (Study 302), were identical in design. The primary objective of each study was to evaluate the efficacy of monthly doses of aducanumab in the treatment of patients with early Alzheimer's disease; each was a randomized, double-blind, placebo-controlled, parallel-arm study with an initial placebo-controlled period of 78 weeks to be followed by a long-term extension up to 5 years. The primary efficacy parameter was the change from baseline to Week 78 in Clinical Dementia Rating Scale – Sum of Boxes score. Secondary efficacy parameters included the change from baseline to Week 78 in Mini-Mental Status Examination, 13-item Alzheimer's Disease Assessment Scale – Cognitive, and

Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale scores. Biomarker-based outcome measures were to include: amyloid positron emission tomographic signal; several measures derived from volumetric brain magnetic resonance imaging; and others. Safety measures were to include adverse events, vital signs, electrocardiograms, safety laboratory tests, anti-aducanumab antibody titers, brain MRI, and a suicidality assessment.

Studies 301 and 302 were discontinued on March 21, 2019, after a prespecified interim futility analysis indicated that the prespecified criteria for futility were met and that those studies were unlikely to meet their primary endpoint on completion. The interim analysis of futility included all data available as of December 26, 2018, for all study patients randomized at least 78 weeks prior to that date. The results of that analysis led to both studies being discontinued on March 21, 2019.

Subsequent efficacy analyses, based on data available through March 20, 2019, had yielded results that questioned the earlier assessment of futility. Those subsequent efficacy analyses and the next steps to be taken were discussed at a face-to-face Type C meeting between the Agency and sponsor on June 14, 2019. At that meeting, it was recommended to the sponsor that further analyses of the efficacy data for Studies 301 and 302 be conducted under a collaborative workstream between the Agency and sponsor. It was also conveyed to the sponsor that there were five options (or conclusions) that might follow the additional analyses to be conducted under that collaborative workstream.

1. Adequate evidence exists that aducanumab is ineffective.

2. The results of Study 302 establish the effectiveness of aducanumab, with Study 301 providing supportive data, so that a standard (full approval) for aducanumab could be considered.

3. The results of Study 302 establish the effectiveness of aducanumab, with Study 301 not providing supportive data, but with the results of Study 301 being sufficiently well understood to be dismissible; a standard (full approval) for aducanumab could again be considered.

4. Accelerated approval of aducanumab may be considered based on a persuasive effect in reducing brain amyloid accompanied by a reasonable likelihood of clinical benefit based on the available clinical results.

5. An additional clinical study of aducanumab should be conducted based on a suggestion of clinical effectiveness seen thus far in the clinical development program, that after further exploration and consideration, proves inadequate to independently establish effectiveness.

Since the Type C meeting on June 14, 2019, additional analyses of the results of Studies 301 and 302 have been conducted jointly by the Agency and sponsor under a collaborative workstream. Those analyses have been conducted in two waves first agreed upon at a meeting held on July 2, 2019:

- Wave 1: To determine whether early termination of Studies 301 and 302 may have impacted the interpretation of efficacy data for those studies and to determine which dataset was appropriate to use for the additional analyses to be conducted in Wave 2.

- Wave 2: To understand the consistency of and differences in the efficacy results of Studies 301 and 302.

Waves 1 and 2 were to be followed by Wave 3 which was to consider which of the five options presented to the sponsor at the Type C meeting held on June 14, 2019, were supported by the outcomes of Waves 1 and 2.

Waves 1 and 2 are now complete and the results of the analyses conducted under those waves are presented for further discussion in the current meeting package. The options under Wave 3 are to be discussed at the current meeting.

FDA sent Preliminary Comments to Biogen on October 18, 2019.

2. DISCUSSION

Question 1: Based on the results and the joint conclusions from the Collaborative Workstream, what does the Agency advise as the appropriate next steps for the development of aducanumab?

FDA Response to Question 1:

Based on the analyses conducted since the June 14, 2019, Type C meeting, we agree that the results of Studies 301 and 302 are interpretable and suitable for additional consideration.

Accordingly, and in the context of the unique nature of the conclusion of Studies 301 and 302, you have presented, on face, the results of a trial of aducanumab in the treatment of Alzheimer's disease (Study 302) that met its primary endpoint.

Equally, you have presented, on face, the results of a trial of aducanumab in the treatment of Alzheimer's disease (Study 301) that did not meet its primary endpoint.

The analyses conducted since the June 14, 2019, Type C meeting, have established not only that the results of Studies 301 and 302 are interpretable, but on face, suggest an understanding of the discordant results of Studies 301 and 302 sufficient to allow for independent consideration of whether Study 302 might provide evidence adequate to establish the effectiveness of aducanumab for the treatment of Alzheimer's disease.

As noted in the final minutes of the June 14, 2019, Type C meeting, "If the results of Study 302 as apparently demonstrated by the "final" analyses are not confounded by the elements described above, it is possible, on face, that the effects of aducanumab in that study might not only be interpreted as being supportive of the efficacy of that compound in Alzheimer's disease, but might also be considered exceptionally persuasive on several of the instruments used to evaluate efficacy." It now appears that this is a reasonable characterization of the results of Study 302.

A single trial can be the basis for marketing approval under specific circumstances discussed in the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (available at the following link on the FDA website – https://www.fda.gov/media/71655/download).

The acceptability of a single trial to support drug approval depends on the study results and cannot be determined prospectively.

Therefore, whether the results of Study 302 might provide evidence adequate to establish the effectiveness of aducanumab for the treatment of Alzheimer's disease (i.e., to support approval), is necessarily a matter of detailed review. Importantly, it is critical to note that we do not see the results of Study 302 as clearly unacceptable in this regard.

As noted in the final minutes of the June 14, 2019, Type C meeting when discussing options 2 and 3, "The submission of a marketing application for aducanumab based primarily on the results of Study 302 as a single positive efficacy study may also be considered. It is possible that the results of Study 301 may have a role in supporting the results of Study 302 or may be understood well enough to be dismissible (i.e., to not represent evidence that the drug is ineffective), assuming that further analyses do not lead to a conclusion that Study 301 is clearly negative. However, currently available data do not suggest the future use of Study 301 as an efficacy study providing independent evidence of effectiveness supporting the approval of aducanumab for the treatment of Alzheimer's disease. For both options 2 and 3, the results of further detailed analyses would be expected to be critical supportive components that establish or contribute to the interpretability of the efficacy results."

Whether the results of Study 301 may have a role in supporting the results of Study 302 is a matter for detailed review, but it appears reasonable, based on the

information you have provided in the meeting materials, to view the results of Study 301, at a minimum, as sufficiently well understood as to not preclude further detailed consideration of the results of Study 302.

Thus, when considering the options discussed at the June 14, 2019, Type C meeting, it appears that the analyses conducted since that meeting and discussed in the meeting materials indicate that options 2 and 3, or a hybrid of both options 2 and 3, are the most appropriate path forward (i.e., as discussed above, it is possible that Study 302 might provide evidence adequate to establish the effectiveness of aducanumab for the treatment of Alzheimer's disease, the results of Study 301 are sufficiently well understood as to not preclude further detailed consideration of the results of Study 302, and it is possible that the results of Study 301 may be supportive of the results of Study 302).

Further consideration of all these issues is necessarily a matter of detailed review.

Therefore, based on the information you have provided in the meeting materials, it appears that planning for submission of a marketing application is a reasonable option.

We look forward to discussing these issues with you at the upcoming meeting.

Meeting Discussion:

The meeting began with the sponsor presenting a set of slides that summarized the analyses conducted under the collaborative workstream. These slides were intended to supplement the contents of the meeting package. During that presentation, there were clarifying questions, answers, and comments provided by the Agency and the sponsor.

After the presentation, the Agency conveyed the following to the sponsor, while again emphasizing the objectives of Waves 1 and 2 of the collaborative workstream analyses:

- Neither Wave 1 nor Wave 2 included a conventional inferential analysis. Wave 2 was not a statistical exercise that was intended to provide statistically persuasive evidence of effectiveness. While noting that the studies were terminated prematurely, the outcome of Wave 1 established that the prespecified outcome(s) of the studies are valid and that the results of the studies are interpretable. The results for Study 302, as supported by collaborative workstream analyses, are noteworthy. Additional collaborative workstream analyses indicated that the results for Study 301 were unlikely to preclude further detailed consideration of the results of Study 302.

- It is unclear whether analyses of the available data for Study 301 (including analyses that are additional to those conducted thus far under the collaborative workstream) will provide support for the existing results for Study 302; however, collaborative workstream analyses conducted thus far indicate that aspects of Study 301 might support the results of Study 302.

- It is possible that the results of the ongoing Phase 1b study of aducanumab, Study 221AD103 (Study 103), may provide further support for the existing results of Study 302.

- Whether Study 302 could serve as a single adequate and well-controlled study that provides substantial evidence of the efficacy of aducanumab in the treatment of Alzheimer's disease will be a matter of review.

- The proposed aducanumab "re-dosing study" described in Slide 25 of the sponsor's presentation at the meeting may provide useful information, and the Agency is open to reviewing the protocol for that study prior to its initiation; this open-label uncontrolled study is to investigate the long-term safety and effectiveness of aducanumab in subjects who were enrolled in Studies 301, 302, 103, and 221AD205 at the time studies of aducanumab were halted earlier this year.

The sponsor clarified that the new statistical analysis plan proposed in outline in Slide 24 of the sponsor's presentation at the meeting applied to both Study 301 and Study 302.

The Agency biometrics reviewer had several specific concerns about the data presented by the sponsor. Those concerns included the following examples, among others:

- Table 31 on Page 108 of the meeting package appeared to show an increasing effect of aducanumab, relative to placebo, on the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) with increasing dose threshold in Study 301. However, that table also appeared to indicate that the mean worsening on the CDR-SB in the placebo group closely accompanied an increasing dose threshold in that table. Thus, any inference that aducanumab had increasing efficacy with increasing dose threshold in that study was confounded by the accompanying mean worsening in the placebo group on the CDR-SB.

- Slide 18 in the sponsor's presentation compared the mean change from baseline in CDR-SB in Studies 301 and 302 between a subset (of aducanumab-treated subjects) consisting of subjects who received ≥ 10 infusions of aducanumab each in a dose of 10 mg/kg with the entire placebo group. The statistical reviewer pointed out that the aducanumab group used in this comparison had been

selected based on a post-randomization event and that the two treatment groups were therefore not comparable.

The sponsor acknowledged not having investigated the use of propensity scores or other methods to ensure that aducanumab dose subsets were compared to a balanced control group. The biometrics reviewer indicated that the use of such methods was important since the creation of subsets based on a post-randomization characteristic tends to counter the balancing effects of randomization and thus confound ability to attribute differences between treatment groups to a single cause such as the intervention under investigation.

Several considerations pertaining to the submission of a Biologics Licensing Application (BLA) for aducanumab that were outlined in Slide 26 of the sponsor's presentation were briefly discussed further. The Agency indicated that one or more of the options presented by the sponsor in that slide such as a rolling review submission, the use of aducanumab's current Fast Track Designation status for further engagement with the Agency, or the submission of a Pre-BLA meeting request may be feasible, but the Agency would need to consider more details of those options before advising the sponsor further.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended*

Pediatric Study Plans.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

SECURE EMAIL COMMUNICATIONS

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4.0 ISSUES REQUIRING FURTHER DISCUSSION

[Identify any issues that remain open at the end of the meeting and require further discussion at a later date. If none exist, please indicate that there were no issues requiring further discussion]

5.0 ACTION ITEMS

[Insert any action items that were identify during the meeting. Include who is responsible to complete the action item and the due date. Responsible party should not be an individual, but either sponsor or FDA. Consider the use of a table to present the information]

Action Item/Description	Owner	Due Date
[Insert action item with a brief description, if applicable]	FDA	[Insert date]
[Insert action item with a brief description, if applicable]	Sponsor	[Insert date]

6.0 ATTACHMENTS AND HANDOUTS

[Identify any attachments or handouts used during the discussion at the meeting. Generally, a copy of presented slides should be attached. If there are no attachments,

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM H Dunn
11/19/2019 05:17:58 PM

IND 106230

MEETING MINUTES

Biogen, Inc.
Attention: Angela M. Neufeld, MS
Associate Director, Global Regulatory Sciences
225 Binney St.
Cambridge, MA 02142

Dear Ms. Neufeld:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for aducanumab.

We also refer to the meeting between representatives of your firm and the FDA on June 14, 2019. The purpose of the meeting was to discuss data and analyses from the two recently terminated Phase 3 clinical trials of aducanumab.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact E. Andrew Papanastasiou, Regulatory Project Manager by email at emilios.papanastasiou@fda.hhs.gov or by phone at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology Products
Deputy Director (Acting)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	C
Meeting Category:	Guidance
Meeting Date and Time:	June 14, 2019, from 9:00 AM to 11:00 AM
Meeting Location:	FDA White Oak Building 22 Room 1415
Application Number:	IND 106230
Product Name:	Aducanumab (BIIB037)
Indication:	Alzheimer's Disease
Sponsor Name:	Biogen, Inc.

FDA ATTENDEES

Billy Dunn, MD, Director, Division of Neurology Products (DNP)
Eric Bastings, MD, Deputy Director, DNP
Nick Kozauer, MD, Associate Director, DNP
Ranjit Mani, MD, Clinical Reviewer, DNP
Kun Jin, PhD, Biostatistics Team Leader
Tristan Massie, PhD, Statistical Reviewer
Kevin Krudys, PhD, Senior Clinical Analyst, DNP
E. Andrew Papanastasiou, MS, PharmD, Regulatory Project Manager, DNP
Sue Jane Wang, PhD, Associate Director, Office of Biostatistics
Thomas Permutt, PhD, Associate Director, Office of Biostatistics

SPONSOR ATTENDEES

Biogen

Alfred Sandrock, MD, PhD, Executive Vice President, Chief Medical Officer
Samantha Budd Haeberlein, PhD., Vice President, Clinical Development
Carmen Castrillo-Viguera, MD, Medical Director, Clinical Development
Christian von Hehn, MD, PhD., Medical Director, Clinical Development
Spyros Chalkias, MD, Medical Director, Drug Safety
Angela Neufeld, MS, Director, Global Regulatory Sciences
Ying Zhu, PhD, Distinguished Biostatistician, Biostatistics
Ying Tian, PhD, Director, Biostatistics
Tianle Chen, PhD, Principal Biostatistician, Biostatistics
Craig Mallinckrodt, PhD, Senior Director, Biostatistics
Xiaopeng Miao, PhD, Associate Director, Biostatistics
Raj Rajagovindan, PhD, Associate Director, Development Imaging

Kumar Kandadi Muralidharan, MS, Associate Director, Pharmacometrics
LeAnne Skordos, PharmD, Director, Clinical Program Leadership
Liz Miller, MS, Associate Director, Medical Writing

Eisai

Martin Rabe, MSc, Vice President, Global Regulatory Strategy
Michael Irizarry, MD, Vice President, Clinical Research

1.0 BACKGROUND

This meeting package discusses analyses of two recently terminated Phase 3 clinical trials of aducanumab (BIIB037). Those Phase 3 studies (Studies 221AD301 and 221AD302) were discontinued after a prespecified interim futility analysis indicated that those studies were unlikely to meet their primary endpoint on completion.

BIIB037 is a humanized monoclonal antibody to β-amyloid that is being developed for the treatment of early Alzheimer's disease.

Studies 221AD301 and 221AD302 were identical in design. The primary objective of each study was to evaluate the efficacy of monthly doses of aducanumab in the treatment of patients with early Alzheimer's disease; each was a randomized, double-blind, placebo-controlled, parallel-arm study with an initial placebo-controlled period of 76 weeks to be followed by a long-term extension up to 5 years. Those to be enrolled in each study were men and women aged 50 to 85 years who satisfied the following main criteria: mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease (NIA-AA criteria); Clinical Dementia Rating Scale global score of 0.5; Repeatable Battery for Assessment of Neuropsychological Status Delayed Memory Index score ≤ 85; Mini-Mental Status Examination score 24 to 30 (inclusive); and positive brain amyloid positron emission tomography. 1605 patients satisfying those criteria were to be enrolled and randomized 1:1:1 to three treatment groups: high-dose aducanumab; low-dose aducanumab; and placebo. The primary efficacy parameter was the change from baseline to Week 78 in Clinical Dementia Rating Scale – Sum of Boxes score. Secondary efficacy parameters included the change from baseline to Week 78 in Mini-Mental Status Examination, 13-item Alzheimer's Disease Assessment Scale – Cognitive, and Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale scores. Biomarker-based outcome measures were to include: amyloid positron emission tomographic signal; several measures derived from volumetric brain magnetic resonance imaging; and others. Safety measures were to include adverse events, vital signs, electrocardiograms, safety laboratory tests, anti-aducanumab antibody titers, brain MRI, and a suicidality assessment.

A mixed model for repeated measures approach was to be used for the efficacy analyses. A sequential closed testing procedure was to be used to compare the

aducanumab groups with the placebo groups during analysis of the primary and secondary efficacy measures, so as to preserve the overall Type I error.

A prespecified independent interim analysis of futility was to be conducted when about 50% of study subjects had the opportunity to complete the Week 78 visit for both Study 221AD301 and Study 221AD302. The studies were not to be considered futile unless both studies had conditional power for the primary efficacy analysis that is < 20% in both the high- and low-dose treatment groups. Other data in addition to the prespecified futility criteria were to be considered.

The interim analysis of futility included all data available as of December 26, 2018, for all study patients randomized least 78 weeks prior to that date. The results of that analysis led to the conclusion that the criteria for futility were met and both studies were then discontinued on March 21, 2019. However, subsequent efficacy analyses based on data available through March 20, 2019, have complicated the earlier assessment of futility. Those additional analyses have led the sponsor to seek a discussion with the Agency of the results of those analyses and the next steps to be taken.

FDA sent Preliminary Comments to Biogen on June 5, 2019.

2.0 DISCUSSION

Question 1: Based on the critical and time sensitive nature of the advice we seek to potentially further drug development for Alzheimer's disease, what does the division leadership advise us to do as a next step?

FDA Response to Question 1: We have reviewed the material that you have presented in your meeting package. Based on that review, we have several initial questions and requests. These are intended to contribute to a productive discussion of the data that you have already presented in your meeting package. Please note that you may address some or all of these questions and requests prior to the meeting, should you so choose, by submitting your responses via email to the regulatory project manager. If you do so, we will endeavor to consider your responses in advance of the meeting, if time allows.

1. In Section 5 ("Interim Analysis") of the final version of the statistical analysis plan (SAP) for Study 221AD301 and Study 221AD302 (submitted on September 28, 2018 as Serial #305 under this IND), you state the following.

   "The futility decision will primarily be based on the conditional power for the primary efficacy endpoint. The study will not be considered as futile unless both studies 221AD301 and 221AD302 have conditional power for the primary efficacy endpoint less than 20% in both the high-dose and low-dose treatment groups. Given the insufficient knowledge of aducanumab's potential effects on

various functional/cognition endpoints or in certain subgroups at the present time, other data in addition to the pre-specified futility criteria will be considered as well, and the IDMC may recommend the studies to be continued as planned based on the weight of the evidence."

Please see the text that we have underlined in the paragraph above. Were any data additional to the prespecified futility criteria considered in making the futility decision?

2. Please provide us with the names the members of the Independent Data Monitoring Committee (IDMC) for Studies 221AD301 and 221AD302. Please provide the charter, or any other written instructions concerning the futility analysis that may be distinct from the SAP, that was provided to the IDMC. Please clarify who at Biogen received the recommendation from the IDMC and what procedures were employed to consider and act on the recommendation.

3. How does the conduct of these new "final" efficacy analyses, performed in the context of the futility declaration, compare with the conduct of the possible (but unperformed) interim superiority analysis pre-specified in the SAP?

4. The final analyses that you have performed for both studies have been based on a dataset with a cut-off date of April 1, 2019, but data within that dataset were censored after March 20, 2019. Have you repeated those final analyses without censoring data collected after March 20, 2019? How do the results of the two sets of analyses compare?

5. Your final analyses suggest that there were substantial differences between Study 221AD301 and Study 221AD302 in the effects of the high dose of aducanumab on the primary and secondary efficacy parameters. Have you conducted additional analyses to explore the basis for those differences? We are interested in what possible reasons have been identified or are under exploration that might explain, in part or in whole, the differences in the final efficacy analyses high dose groups of Study 221AD301 and Study 221AD302.

6. Have you explored whether differences in demographic and other baseline characteristics, other than those outlined in Table 6 in your meeting package, may explain the differences in the final efficacy analyses high dose groups of Study 221AD301 and Study 221AD302? The meeting package states that there are no major demographic or baseline differences between study arms within each study. We are curious about whether there may be demographic or baseline differences between studies that contribute to the different results in the high dose group of each study.

7. In your briefing package, you state that conditional power for the interim futility analysis was calculated "based on pooled data observed at the interim futility analysis." Please provide further details on how data was pooled for that analysis. Also, please provide conditional power estimates if non-pooled futility analyses had been performed for each study independently. We note that the SAP appears silent on the issue of pooling for the futility analysis.

8. We note that the actual dose received by subjects may have been influenced by dose suspension, modification, or termination for amyloid-related imaging abnormalities (ARIA) events. In addition, protocol amendments throughout the study modified dosing rules for management of ARIA and increased the "high dose" for ApoE4 carriers. We wonder whether there may be some "disadvantage" conferred upon patients enrolled earlier in the study that developed ARIA. We therefore suggest performing analyses to explore the relationship between the actual dose of aducanumab received and clinical endpoints, or sharing with us the results of analyses that you have performed in this regard.

9. We encourage you to explore the relationship between exposure (e.g., dose, and aducanumab concentration), amyloid positron emission tomography standard uptake value ratios, and clinical endpoints.

10. Please clarify the prespecified study closeout plans for collecting additional follow-up on endpoints for patients who had not had the opportunity to complete each study as of March 21, 2019.

Meeting Discussion:

Prior to the meeting, the sponsor had provided responses to the Agency's preliminary comments dated June 5, 2019. Those responses, dated June 10, 2019, are attached to the meeting minutes and their contents are self-explanatory; they were reviewed by the Agency prior to the meeting. The sponsor's responses of June 10, 2019, were supplemented by a slide presentation which was forwarded to the Agency a day in advance of the meeting. That slide presentation file is also attached to the meeting minutes and its contents too are self-explanatory.

The meeting began with the sponsor's slide presentation during which several clarifications were sought by the Agency staff attending the meeting. The Agency urged the sponsor to include data from the low-dose group in the analyses and to consider additional metrics to characterize exposure to aducanumab. There was a shared understanding that performing exploratory analyses in the context of the futility declaration was a unique situation, but appropriate to maximize learnings from such a rich dataset. During the slide presentation and subsequent discussion, the sponsor indicated that additional analyses of the efficacy data for Study 221AD301 (Study 301) and Study 221AD302 (Study 302) were both ongoing and planned.

Further meeting discussion centered on the following issues that the Agency conveyed to the sponsor during the meeting, the discussion of which is reflected in the summaries below.

- Interpretation of the available efficacy results of both Study 301 and Study 302 has been complicated by the sponsor's declaration of futility for both studies (as was publicly announced on March 21, 2019) and concomitant termination of the studies. In the Agency's view, given the interim efficacy analyses for the individual studies presented by the sponsor, the pre-specified plan for the futility analysis was flawed and it would have been more appropriate if futility had not been declared for those studies. The effect of early termination of the studies on the interpretability of the observed efficacy data and associated analyses is a matter for further detailed consideration.

- Further complicating the interpretation of the available data for Studies 301 and 302 are the partially conflicting results of the "final" analyses of efficacy data (i.e., the analyses that included data available through March 20, 2019) for Study 301 as compared with those for Study 302, with particular attention to the discordant high dose results of each study (while noting an apparent degree of consistency of the low dose results between the studies). A detailed understanding, informed by plans for further analyses (see below), of the overall results, and especially these discordant results, is critical to any consideration of whether Study 302 (with or without possible support from Study 301, as might be determined from further explorations of the data) might provide evidence adequate to establish the effectiveness of aducanumab for the treatment of Alzheimer's disease.

- If the results of Study 302 as apparently demonstrated by the "final" analyses are not confounded by the elements described above, it is possible, on face, that the effects of aducanumab in that study might not only be interpreted as being supportive of the efficacy of that compound in Alzheimer's disease, but might also be considered exceptionally persuasive on several of the instruments used to evaluate efficacy.

- For the reasons described above, the development of aducanumab for the treatment of (b) (4) Alzheimer's disease should be continued and not abandoned, as the available data suggest that the drug may be clinically active and do not provide convincing evidence that the drug is ineffective for that indication. There are also data available indicating that aducanumab is a pharmacologically-active molecule, as demonstrated primarily by its effect on brain amyloid.

- Further analyses of the available data for Studies 301 and 302 must be conducted to better understand those results, as the currently available analyses are inconclusive. It is possible that aducanumab is an effective drug for the

treatment of Alzheimer's disease; if that is so, it is imperative that extensive resources be brought to bear on achieving a maximum understanding of the existing data. Given the wholly unique situation that is the current state of the aducanumab development program (i.e., large, international, apparently rigorously conducted, logistically complex studies that were near completion but are now terminated, with a public declaration of futility and termination, but with a large but incomplete, complicated, and partially discordant data set now suggestive of the possible effectiveness of aducanumab for the treatment of Alzheimer's disease), those further analyses would best be conducted as part of a bilateral effort involving the Agency and sponsor; i.e., through a "workstream" or "working group" collaboration. The Agency and sponsor agreed to pursue this approach. An important initial step, agreed to by both the Agency and the sponsor, was for the sponsor to arrange for the prompt provision of the patient-level data sets to the Agency.

- Given the considerable uncertainty at present as to how the results of Study 301 and 302 are to be interpreted, a public presentation of the results of the futility and other efficacy analyses of Studies 301 and 302 that have been made available to the Agency is premature.

- A number of potential options may be available, depending on the results of additional analyses of data for Studies 301 and 302, when viewed in conjunction with those analyses already available. These additional analyses would largely be the focus of the collaborative working group. The following 5 options were discussed:

    - 1 – Adequate evidence exists to conclude that aducanumab is ineffective
    - 2 – Study 302 establishes effectiveness; Study 301 provides supportive data; standard (full) approval
    - 3 – Study 302 establishes effectiveness; Study 301 does not provide supportive data but is understood well enough to be dismissible; standard (full) approval
    - 4 – Accelerated approval based on a persuasive effect on amyloid reduction, accompanied by a reasonable likelihood of clinical benefit based on the available clinical results
    - 5 – Conduct an additional clinical study based on the suggestion of effectiveness seen thus far in the clinical development program that, after further detailed exploration and consideration, proves inadequate to independently establish effectiveness

  These options are further discussed below:

    - 1 – The termination of the clinical development of aducanumab as a treatment for Alzheimer's disease would be predicated on a conclusion

that adequate evidence exists to establish that aducanumab is ineffective (or is highly likely to be ineffective) for the treatment of Alzheimer's disease. For the reasons noted above, that is not the case.

- 2 and 3 – The submission of a marketing application for aducanumab based primarily on the results of Study 302 as a single positive efficacy study may also be considered. It is possible that the results of Study 301 may have a role in supporting the results of Study 302 or may be understood well enough to be dismissible (i.e., to not represent evidence that the drug is ineffective), assuming that further analyses do not lead to a conclusion that Study 301 is clearly negative. However, currently available data do not suggest the future use of Study 301 as an efficacy study providing independent evidence of effectiveness supporting the approval of aducanumab for the treatment of Alzheimer's disease. For both options 2 and 3, the results of further detailed analyses would be expected to be critical supportive components that establish or contribute to the interpretability of the efficacy results.

- 4 – A further possibility that the sponsor may give consideration to, depending on what further analyses demonstrate, is to seek accelerated approval for aducanumab, based on its effects in reducing brain amyloid. Such an approval would be predicated on a conclusion that an effect of aducanumab in reducing brain amyloid is reasonably likely to predict clinical benefit. Presumably, such a conclusion would be supported by the clinical efficacy data that exist in the patients that experienced reduction of brain amyloid. Such an approach would have numerous complicated aspects, was discussed only briefly during the meeting, and, if contemplated further, should be the subject of independent detailed discussion.

- 5 – It is possible that additional detailed analyses of the existing data could contribute to a greater understanding of aducanumab's clinical efficacy profile, but such understanding might be insufficient to independently establish its effectiveness. In such a situation, the sponsor may need to conduct a further efficacy study of aducanumab to provide additional support to the existing data. The approach to such an additional study would be the subject of additional more detailed discussion.

- The Agency also suggested to the sponsor that an analysis of tertiary and exploratory outcomes for Studies 301 and 302 may contribute to an understanding of the effect of aducanumab in those studies.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

4.0 ATTACHMENTS AND HANDOUTS

1. The responses sent by Biogen to the Agency on June 10, 2019, addressing the preliminary comments sent by the Agency to Biogen on June 5, 2019.

2. Materials presented by Biogen at the June 14, 2019, meeting.

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/s/

WILLIAM H Dunn
06/26/2019 10:07:57 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106230

MEETING MINUTES

Biogen Idec Inc.
Attention: Nadine D. Cohen, Ph. D
Sr. Vice President, Regulatory Affairs
225 Binney Street
Cambridge, MA 02142

Dear Dr. Cohen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BIIB037 (aducanumab).

We also refer to the meeting between representatives of your firm and the FDA on December 16, 2014. The purpose of the meeting was to discuss your Phase 3 development plans.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Teresa Wheelous, Sr. Regulatory Project Manager at (301) 796-1161.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology Products0
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: December 16, 2014 11 AM - Noon
Meeting Location: WO 22 Room 1311

Application Number: 106230
Product Name: BIIB037 (aducanumab)
Indication: Treatment of (b) (4) Alzheimer's disease (AD)

Sponsor/Applicant Name: Biogen Idec

FDA ATTENDEES (tentative)
Ellis Unger, MD – ODE I Director
Robert Temple, MD – ODE I Deputy Director
Billy Dunn, MD – Acting Division Director
Eric Bastings, MD – Deputy Division Director
Ranjit Mani, MD – Clinical Reviewer
Teresa Buracchio, MD – Clinical Reviewer
Marjorie Shapiro, PhD – Product Quality Team Leader
Gerald Feldman, PhD – Product Quality Reviewer
Angela Men, PhD – Clinical Pharmacology Team Leader
Jagan Parepally, PhD – Clinical Pharmacology Reviewer
Joshua Hunt, Pharm D – CSS Reviewer
Kun Jin, PhD – Biometrics Team Leader
Tristan Massie, PhD – Biometrics Reviewer
Monica Munoz, PhD - OSE Regulatory Research
Teresa Wheelous, R. Ph. – Sr. Regulatory Project Manager
Nyedra W. Booker, PharmD, MPH – DRISK Reviewer

BIOGEN IDEC ATTENDEES
Joanne Gibbons - Associate Director, Regulatory Affairs
Heather Faulds - Director, Regulatory Affairs
Paula Sandler - Vice President, Regulatory Affairs
Preeti Singh - Senior Manager, Regulatory Affairs
Jeff Sevigny - Senior Medical Director, Clinical Development
Vissia Viglietta - Medical Director, Clinical Development
Yan Ling - Associate Medical Director, Clinical Development

Leslie Williams - Senior Director, Drug Safety
Jim Ferrero - Director, Clinical Pharmacology
Jonathan Tran - Director, Clinical Pharmacology
John O'Gorman - Director, Biostatistics
Ying Zhu - Director, Biostatistics
Norman Kim - Director, Pharmacotoxicology
John Stofko - Vice President, Program Leadership and Management
Ellen Magaziner - Director, Early Stage Pipeline Leadership
Suzanne Murray - Director, Regulatory Affairs
Mary Chiavelli - Senior Manager, Regulatory Affairs
Ethan O'Malley - New Product Leader

BACKGROUND

In a September 26, 2014, meeting request Biogen Idec requested a meeting to obtain concurrence from the Agency regarding the acceptability of the nonclinical, clinical, and CMC plans for registration of BIIB037 for the treatment of (b) (4) AD. The briefing package was submitted on November 13, 2014.

BIIB037 is 12F6A, fully human, IgG1, anti-beta-amyloid monoclonal antibody named (aducanumab).

There are two identical pivotal Phase 3 studies of BIIB037 planned. The primary objective is to evaluate the efficacy of monthly doses of BIIB037 in slowing cognitive and functional impairment. The studies are randomized, double-blind, placebo-controlled, parallel-arm study of (b) (4) duration. Followed by a (b) (4) open-label dose-blinded extension study in which all subjects will receive active treatment. All doses of study drug are to be administered intravenously every 4 weeks.

DISCUSSION

CLINICAL

Introductory Preliminary Agency Comments

Please note that our responses to the questions below are based on our review of your Briefing Package. Should you desire an in-depth review of your proposed Phase 3 protocols, we recommend that a Special Protocol Assessment be requested.

Our responses below take into consideration not only the contents of the Briefing Package submitted on November 14, 2014 (Serial #095), but also the summary of interim analysis results for Study 221AD103 submitted by e-mail on December 4, 2014.

STUDY DESIGN

Question 1

Does the Agency agree with the overall design of the Phase 3 studies, namely:

a. Does the Agency agree that the proposed patient population, as defined by the inclusion/exclusion criteria, is appropriate?

Preliminary FDA Response

The inclusion and exclusion criteria to be used to enroll patients in your two proposed Phase 3 randomized, double-blind, placebo-controlled studies do appear to delineate a population with early Alzheimer's Disease. Based on those criteria, patients enrolled in those studies will, at entry, range in their severity of impairment from those with Mild Cognitive Impairment due to Alzheimer's Disease (prodromal Alzheimer's Disease) to mild dementia due to Alzheimer's Disease (with both underlined entities conforming to the National Institute on Aging – Alzheimer's Association criteria).

Meeting Discussion

The sponsor expressed the view that the application of the inclusion criteria currently proposed for the two Phase 3 efficacy studies is likely to lead to each study population consisting largely of patients with Mild Cognitive Impairment due to Alzheimer's Disease (prodromal Alzheimer's Disease) with only a very small proportion of those enrolled having mild dementia due to Alzheimer's Disease. On that basis, and given the current consensus that Mild Cognitive Impairment due to Alzheimer's Disease and mild dementia due to Alzheimer's Disease are part of a continuum, the sponsor contended that the CDR-SB may indeed be an appropriate sole primary efficacy measure for both studies.

The Agency agreed fully that a sharp distinction between Mild Cognitive Impairment due to Alzheimer's Disease and mild dementia due to Alzheimer's Disease might frequently not be possible, but was concerned that the CDR-SB is not capable of independently evaluating cognition and function when activities of daily living are more impaired, as might be expected in patients with mild dementia due to Alzheimer's Disease. The Agency further observed that the currently proposed inclusion criteria for both Phase 3 studies would not preclude the enrollment in significant proportions of patients with mild dementia due to Alzheimer's Disease, in whom the CDR-SB is not appropriate to use as a sole primary efficacy measure. However, the CDR-SB may still be appropriate for use as an only primary efficacy measure in both studies should the proportion of patients with mild dementia in those studies be very small.

The Agency did confirm (as was already stated in the Preliminary Response to Question 14) that a product could be approved for the treatment of (b) (4) Alzheimer's Disease (or for a similar indication) based on two positive adequate and well-controlled studies conducted in patients with (b) (4) Alzheimer's Disease only (using the CDR-SB as on the sole primary efficacy measure), or on the basis of a single positive adequate and well-controlled study in patients with (b) (4) Alzheimer's Disease (with the CDR-SB used as a sole primary efficacy measure) and a single positive adequate and well-controlled study in patients with (b) (4) Alzheimer's Disease (in which the efficacy of BIIB037 is demonstrated separately on cognitive and functional co-primary efficacy measures).

Based on the interim analysis of efficacy and safety data for the Phase 1b study 221AD103, the sponsor is also considering [redacted] The Agency had no objection in principle to that proposal; however, the Agency also observed that should only one of the two studies then be positive, and the other study negative, for efficacy (and assuming that the primary efficacy measures used in those studies are appropriate), such results would not ordinarily support the approval of BIIB037 for an indication similar to that which the sponsor is currently pursuing. [redacted]

The Agency also noted that if, under the above proposal, different doses or ranges of doses of BIIB037 were evaluated in each of the two studies, it could prove difficult to draw conclusions regarding the efficacy or safety of a specific dose (or range of doses) of BIIB037 in a population in which that dose (or range of doses) had not been evaluated. [redacted] The Agency had no objection to the pooling of efficacy data across doses of BIIB037 for analysis purposes, as long as the details of that pooling strategy were specified prospectively. The Agency cautioned, however, that the interpretation of the results of pooled analyses may not be straightforward and that pooling across doses may be ill-advised if there were differences in efficacy based on dose.

b. Does the Agency agree that the proposed study duration, including [redacted] of placebo-controlled treatment and a follow-up period of 18 weeks, is appropriate?

Preliminary FDA Response

The pertinent data that are currently available (including information provided in your Briefing Package) suggest that the planned duration of the treatment and follow-up phases for each randomized, double-blind, placebo-controlled Phase 3 study of BIIB037 may be appropriate.

Meeting Discussion

The sponsor has interpreted the interim results of the Phase 1b study 221AD103 as suggesting that a study duration of [redacted] may suffice for demonstrating a treatment effect of BIIB037 in the planned Phase 3 studies and proposed that an interim efficacy analysis be conducted at [redacted] timepoint. The Agency cautioned that the interim analysis proposed by the sponsor would result in the prior expenditure of part of the alpha

that would ordinarily be proposed for the final analysis. The Agency did not, however, object to the Phase 3 efficacy studies of BIIB037 being limited in duration to (b) (4). In fact, the Agency currently requires that studies that are directed at demonstrating that a product has efficacy in the treatment of Alzheimer's Disease need only last 3 to 6 months.

c. Does the Agency agree that the proposed primary endpoint is appropriate to demonstrate a clinically meaningful effect of BIIB037 in (b) (4) AD, and as such, an acceptable measure of efficacy for the Phase 3 studies?

Preliminary FDA Response

The population that you plan to enroll in your Phase 3 studies will have impaired cognition (that is confined in some patients to an impairment of memory alone) and at least mild impairment of daily functioning in a significant proportion. Accordingly, the primary efficacy measure or measures that you use in those studies should be capable of demonstrating that BIIB037 has a beneficial effect on cognition as well as an independent beneficial effect on function; evidence that BIIB037 has an independent beneficial effect on function is required so that it may be established that any beneficial effect of that product on cognition (as assessed by sensitive measures of neuropsychological performance that are of uncertain independent clinical meaning) is clinically meaningful. In our judgment, the properties of the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) are such that the instrument is capable of demonstrating independent beneficial effects on both cognition and function in patients who have Mild Cognitive Impairment due to Alzheimer's Disease (prodromal Alzheimer's Disease), but is increasingly less capable of demonstrating that those two effects are independent once functional impairment becomes more pronounced as would be expected in those with mild dementia due to Alzheimer's Disease, and is thus not well suited for use as a sole primary efficacy measure in the patients with mild dementia of the Alzheimer's type, who are also to be enrolled in each of your Phase 3 studies. At the current time, we are unaware of a single composite instrument that is suitable for use as a sole primary efficacy measure in patients with mild dementia due to Alzheimer's Disease, and given the lack of such an instrument, the efficacy of BIIB037 in that population should be demonstrated separately on cognitive and functional co-primary efficacy measures, as has been the standard approach with previous development programs in this stage of disease.

Please also see our response to Question 14.

Meeting Discussion

Please refer to the meeting discussion summarized under Question 1a.

d. Does the Agency agree with the proposed secondary endpoints and that the results, if found to be statistically significant, will be included in the clinical efficacy section of the label?

Preliminary FDA Response
We have no objection to the use of the secondary clinical and biomarker efficacy endpoints that you have proposed for your Phase 3 trials. However, should you wish to include results that are based on the analysis of those measures in the Prescribing Information for BIIB037, the following criteria should be satisfied.

- The secondary efficacy measures whose analyses you wish to include in labeling should be prospectively specified.

- The prospectively-specified statistical analysis plan for those secondary efficacy measures should include methods for preserving the Type I error, as appropriate.

- The results of the analyses of the secondary efficacy measures that are prospectively specified for inclusion in labeling will ordinarily need to be independently substantiated.

- Agreement should be reached a priori with this Division as to which secondary efficacy measures are appropriate to include in labeling. Such measures should address domains other than those covered by the primary efficacy measures.

Meeting Discussion
None

e. Does the Agency agree with the ordering of the secondary endpoints?

Preliminary FDA Response
While the Briefing Package indicates that a sequentially closed testing procedure will be used for analysis of the secondary endpoints, you do not, as best as we are able to determine, state the specific order in which the individual secondary efficacy endpoints will be analyzed. We do not, however, object in principle to a sequential closed testing procedure being used for the analysis of clinical secondary efficacy endpoints. Please also see our response to Question 1d.

Given the current lack of a scientific consensus as to which biomarker outcome measure (or set of such measures) might be most appropriate for helping confirm that a compound is (b) (4) in Alzheimer's Disease, the inclusion of the analysis of a specific biomarker-derived measure (such as the extent of brain amyloid as demonstrated on positron emission tomography) in a hierarchical sequence of analyses of clinical plus biomarker measures combined, or the specification of a hierarchical analysis of several biomarker-based outcome measures alone, is premature. Instead, you should pre-specify a separate detailed statistical analysis plan for the outcome measure that is to be derived from brain amyloid imaging, as well as for every other biomarker-derived outcome measure that you may propose to use in your Phase 3 studies of BIIB037 to provide evidence that the same compound is (b) (4). Such an arrangement will allow for the possibility that if an expert consensus is later reached that a specific biomarker-derived outcome measure (or combination of such measures) is the most

appropriate for supporting a claim that a compound is [redacted](b) (4)" in Alzheimer's Disease, a pre-specified detailed plan will already exist for its analysis.

Please also see our comments in response to Question 5.

Meeting Discussion
The Agency confirmed its recommendation that a separate detailed analysis plan be prospectively described for each biomarker-derived efficacy outcome measure to be used in Phase 3 studies of BIIB037. The Agency also confirmed its view that if several biomarker-derived outcome measures are proposed for use in those studies, a hierarchical sequence for their analysis should not be specified. Further, the Agency does not believe it is of significance whether specific biomarker-derived outcome measures are designated as secondary or tertiary outcome measures. The Agency's views in this regard are based on the current lack of an expert consensus as to which biomarker-derived outcome measures may be appropriate for use in support of a claim for [redacted](b) (4); a statistical penalty cannot therefore be justified for the analysis of those measures.

f. Does the Agency agree with the proposed plan for safety monitoring, specifically with respect to ARIA?

Preliminary FDA Response
We note with concern the extent and severity of the amyloid-related imaging abnormalities, as well as the severity of the associated clinical symptoms in some patients, that have been observed fairly early during the clinical development of BIIB037. However, based on our review of the pertinent data in this Briefing Package, your proposed plan for safety monitoring during your Phase 3 trials appears acceptable.

Meeting Discussion
None

DOSE SELECTION
Question 2
Does the Agency agree with the proposed target dose and titration regimen for Phase 3?

Preliminary FDA Response
[redacted](b) (4)

(b) (4)

You also propose that (in your Phase 3 studies) the dose of BIIB037 be titrated as follows in an effort to reduce the incidence and severity of amyloid-related imaging abnormalities: (b) (4) for the remainder of the study. Whether that titration regimen will indeed serve to minimize the incidence and severity of amyloid-related imaging abnormalities remains to be determined, but is being evaluated in the ongoing Phase 1b study 221AD103.

We are uncertain if the apparent effect of BIIB037 on brain amyloid that was demonstrated on positron emission tomography in Study 211AD103 will be predictive of its efficacy (especially on a clinical outcome) in Phase 3, but do not object to the use of the former effect to select the BIIB037 dose (or doses) for further investigation in Phase 3. We do strongly urge, though, that the efficacy of a range of doses of BIIB037 (e.g., (b) (4) each administered every 4 weeks), rather than the efficacy of only a single BIIB037 dosing regimen, be evaluated in Phase 3. The evaluation of at least 2 separate BIIB037 dosing regimens in Phase 3 would be useful if, for example, the (b) (4) dose of BIIB037, used alone and administered every 4 weeks, is demonstrated to have efficacy, but is at the same time poorly tolerated. A further advantage in evaluating the efficacy of a range of doses of BIIB037 in Phase 3, rather than a single dose, is that a dose-response observed under those conditions may also be supportive of the efficacy of BIIB037 in the study population.

We have also noted the results of the interim analysis of CDR-SB and Mini-Mental Status Examination (MMSE) scores in Study 211AD103 that you submitted on December 4, 2014. Those results, based as they are on the administration of each dose of BIIB037 to only a small number of patients, are limited in their usefulness in predicting what dose or doses of that product may eventually be effective in Phase 3 studies. While keeping in mind that limitation, we note that the 3 mg/kg dose of BIIB037, administered every 4 weeks, is reported to have been beneficial in comparison with placebo, when its efficacy was evaluated using the change from baseline to Week 52 in MMSE score; that observation may provide at least some further support for the evaluation of a range of BIIB037 dosing regimens, (b) (4) in Phase 3.

Meeting Discussion
Please refer to the meeting discussion summarized under Question 1a.

CONFIRMATION OF AMYLOID PATHOLOGY

Question 3

Does the Agency agree that the proposed approach of using CSF Aβ42 measurements (e.g., (b) (4)) for enrichment of a subset of subjects is appropriate for the Phase 3 studies?

Preliminary FDA Response
We agree with that proposal.

Meeting Discussion
None.

REGISTRATION PROPOSAL
Question 4
Does the Agency agree that achievement of superiority in the proposed Phase 3 studies would support the following indication statement, if acceptable safety and statistically significant efficacy are demonstrated in the proposed Phase 3 studies?

(b) (4)

Preliminary FDA Response
Please see our response to Question 5.

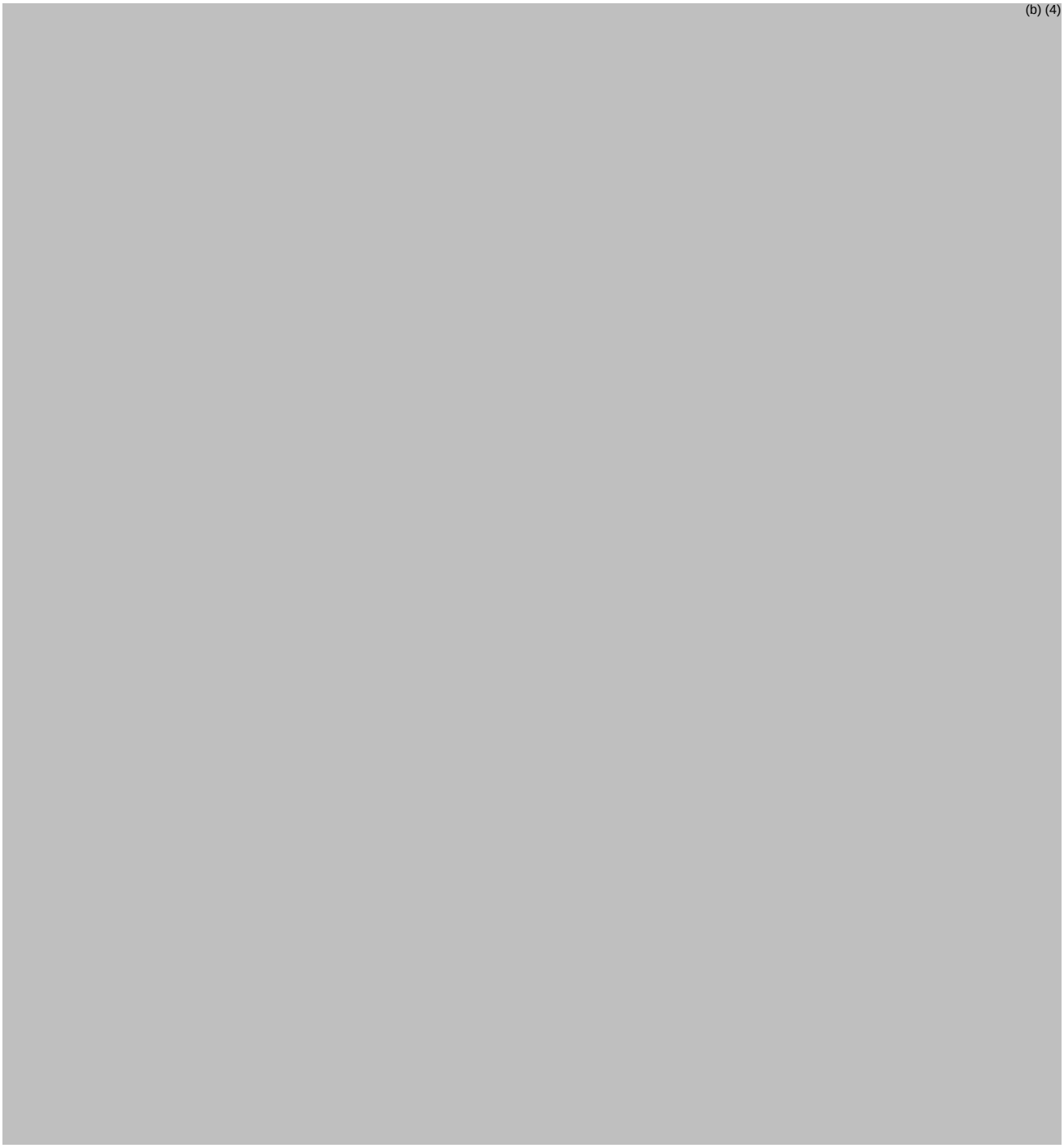
Meeting Discussion
None.

(b) (4)
Question 5
Does the Agency agree that a claim of (b) (4) **would be supported by demonstration of a statistically significant effect on the primary endpoint,** (b) (4) **in a sub-set of subjects in the Phase 3 studies as proposed?**

Preliminary FDA Response
We understand the rationale for your proposed use of a combination of a statistically significant effect on the clinical primary efficacy parameter (i.e., (b) (4)) and (b) (4)) in a patient subset, and a correlation between the two outcomes as the basis for seeking a claim that BIIB037 is "(b) (4)" in early Alzheimer's Disease. However, we are not currently able to endorse that proposal, as is further explained below.

(b) (4)

(b) (4)



SAFETY DATABASE

Question 6

Does the Agency agree that the projected overall safety database is adequate for registration?

Preliminary FDA Response

Yes.

Meeting Discussion
None.

PEDIATRIC WAIVER
Question 7
Does the Agency agree that a full pediatric waiver is appropriate for this indication?

Preliminary FDA Response
Yes.

Meeting Discussion
None.

NONCLINICAL
Question 8
Does the Agency agree that the non-clinical toxicology studies are adequate to support the registration of BIIB037?

Preliminary FDA Response
We agree that the completed general toxicology studies appear to be sufficient to support a marketing application for BII037. However, the adequacy of those studies will be a matter of review.

Meeting Discussion
None.

Question 9
Does the Agency agree that the completed nonclinical toxicity studies adequately assess the carcinogenicity risk of BIIB037, and that no further carcinogenicity studies are required?

Preliminary FDA Response
Although we agree that standard carcinogenicity bioassays are generally not appropriate for therapeutic monoclonal antibodies, you should submit a request for waiver of carcinogenicity studies to the IND. The waiver request should include a detailed rationale, with any supportive data, for your claim that carcinogenicity studies of BIIB037 will not provide useful safety information.

Meeting Discussion
None.

Question 10
Does the Agency agree that a formal assessment of abuse liability is not required for BIIB037?

Preliminary FDA Response

In determining if a drug (or a biologic, as in this instance) needs to be studied for its abuse potential, CSS relies on the principles described in the Draft Guidance for Industry entitled "*Assessment of Abuse Potential of Drugs*" (2010) for general guidance (an example is the description in that document of *in vitro* receptor binding studies typically conducted for drugs that are active on the central nervous system [CNS]). That Draft Guidance document is available at the following link:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf).

As stated in that Draft Guidance, the abuse potential of a drug needs to be fully assessed if the drug has an effect on the CNS, is chemically or pharmacologically similar to other drugs with known abuse potential, or produces psychoactive effects such as sedation, euphoria, and mood changes. BIIB037 is not chemically or pharmacologically similar to any other drug with known abuse potential, but is intended to have effects on the CNS. Therefore, as part of your safety analysis, you should monitor for adverse events that may indicate a potential for abuse of BIIB037 during clinical trials that are conducted in all phases of development of that compound.

Meeting Discussion
None.

CLINICAL PHARMACOLOGY
Question 11
Does the Agency agree with the proposed clinical pharmacology plan to support registration, including:

a) **Does the Agency agree that no additional QTc studies are necessary?**

   Preliminary FDA Response
   Yes.

   Meeting Discussion
   None.

b) **Does the Agency agree with proposed plan to assess drug-drug interactions?**

   Preliminary FDA Response
   Yes.

   Meeting Discussion
   None.

Additional Clinical Pharmacology Comments

- You should provide adequate analytical characterization demonstrating the comparability of the product used in Phase 1 studies (BIIB037-A) and that to be used in Phase 3 studies

(BIIB037-B). Otherwise, a clinical comparability study of the two products should be conducted.

- You should develop an immunogenicity assay to identify binding and neutralizing antibodies to BIIB037. Further, you should evaluate the impact of immunogenicity on the pharmacokinetics, pharmacodynamics, and safety of BIIB037 in your proposed Phase 3 studies.

- You should provide justification for the use, in clinical trials, of doses of BIIB037 that are calculated according to subject weight (i.e., mg/kg dosing) as opposed to fixed doses of that compound.

Meeting Discussion
None.

CHEMISTRY, MANUFACTURING, AND CONTROLS
Question 12
Does the Agency agree that the data presented and the analytical comparability plan will be sufficient to demonstrate that the Drug Substance and Drug Product produced using the BIIB037-A and BIIB037-B manufacturing processes are comparable?

Preliminary FDA Response
We agree that your proposed plan appears to be sufficient to demonstrate comparability between BIIB037 Drug Substance and Drug Product manufactured by either the BIIB037-A or the BIIB037-B processes. We note that you had previously committed to add appropriate controls of LMW species (as stated in your submission dated September 19, 2011). Please add quantitative release acceptance criteria for the individual peaks analyzed by icIEF, SEC, and reduced CE-SDS. Acceptance of comparability will be a review issue once the data are submitted to the IND.

Meeting Discussion
The sponsor stated that it was continuing to collect information regarding low molecular weight species, and would provide those data when available. The sponsor asked when the Agency would want that information for review. The sponsor was informed that submission of those data as part of the BLA would be acceptable.

Question 13
Does the Agency concur with the release test specifications for the BIIB037-001 B drug substance and drug product to be used in the proposed Phase 3 clinical study?

Preliminary FDA Response
We concur with the proposed release test specifications for BIIB037-B Drug Substance and Drug Product that will be used for in your proposed Phase 3 studies, with the caveats mentioned earlier (please see our response to Question 12). We also note that you had originally agreed to assess sub-visible particles both at release and while on stability (ibid).

Meeting Discussion
None.

OTHER CLINICAL
Question 14
Does the Agency agree that 2 studies as outlined, [redacted] (b) (4), would support an indication for the treatment of patients with prodromal AD?

Preliminary FDA Response
We agree that two positive studies that are similar in design to the Phase 3 studies that you have proposed, [redacted] (b) (4) would be able to support an application for [redacted] (b) (4) Alzheimer's Disease.

Please note that we may also be willing to consider approving a product for the treatment of [redacted] (b) (4) Alzheimer's Disease (or for a similar indication), based on a single positive adequate and well-controlled study in patients with [redacted] (b) (4) and a single positive adequate and well-controlled study in patients with [redacted] (b) (4) It may also be possible for a product to be approved for the treatment of [redacted] (b) (4) Alzheimer's Disease (or for a similar indication) based on two positive adequate and well-controlled studies conducted in patients with [redacted] (b) (4). In either of those circumstances, the precise text of the therapeutic indication to be granted is a matter for future discussion.

Meeting Discussion
See Meeting Discussion under Question 1a.

Question 15
Are there circumstances where a single pivotal study [redacted] (b) (4) would be acceptable to support approval of BIIB037 with a claim of [redacted] (b) (4)?

Preliminary FDA Response
While it is possible that BIIB037 could be approved for the treatment of [redacted] (b) (4) Alzheimer's Disease based on a single adequate and well-controlled efficacy study, such as one of the two Phase 3 randomized, controlled studies that you have described in the current submission, such an approval would in all likelihood occur only under exceptional circumstances: in the vast majority of instances, independent substantiation of that treatment effect in a second adequate and well-controlled trial would be necessary to satisfy the requirement for substantial evidence.

Among the criteria that the Agency will give consideration to in granting approval to any product for the treatment of Alzheimer's Disease, based only on the results of a single study, are the following:

- Evidence of a robust benefit of that product with a clinical effect size much greater than that seen with drugs already approved for the same indication and at a pre-specified level of statistical significance appreciably lower than 0.05.

- Confirmation that the treatment effect of that product as seen on the primary efficacy analysis is also present on additional efficacy analyses of the primary parameters; in addition, analyses of secondary efficacy parameters should all indicate at least a trend towards superiority of active product over placebo.

- An indication that the treatment effect is increasing over time.

A useful rule of thumb for assessing whether any product may be approved for the treatment of Alzheimer's Disease (at any stage of that illness) based on the results of a single efficacy study is that those results are such that they render the conduct of a second study to substantiate them unethical.

The same general considerations as above would apply regardless of whether inclusion in labeling of (b) (4) in Alzheimer's Disease is or is not being sought.

Please refer to the Agency Guidance for Industry, entitled "*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*" (May 1998) for a more comprehensive discussion of this subject. That document, and the following link, have already been cited in our response to Question 5.

http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf

Meeting Discussion
None.

ADDITIONAL ITEMS DISCUSSED AT MEETING

- The sponsor stated that a request for Breakthrough Therapy designation would be submitted for BIIB037.

- The sponsor is to further consider the Agency's recommendations regarding the Phase 3 development plan for BIIB037 in Alzheimer's Disease, and finalize that plan. The mechanism for further communication between the Agency and sponsor during the development of the Phase 3 protocols for BIIB037 was discussed. The Agency indicated that while e-mail exchanges alone were appropriate for minor items not requiring further internal discussion, items for which such discussion might be necessary were best addressed by a full submission to the IND to which the Agency might then respond either in writing alone, or in a teleconference or face-to-face meeting with the sponsor. It was recommended to the sponsor that one or both Phase 3 protocols be submitted to the Agency with a request for Special Protocol Assessment; the Agency added that a failure to reach agreement after a Special Protocol Assessment would not preclude the use of that protocol as a key efficacy study.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting

mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number

b. Principal investigator
c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

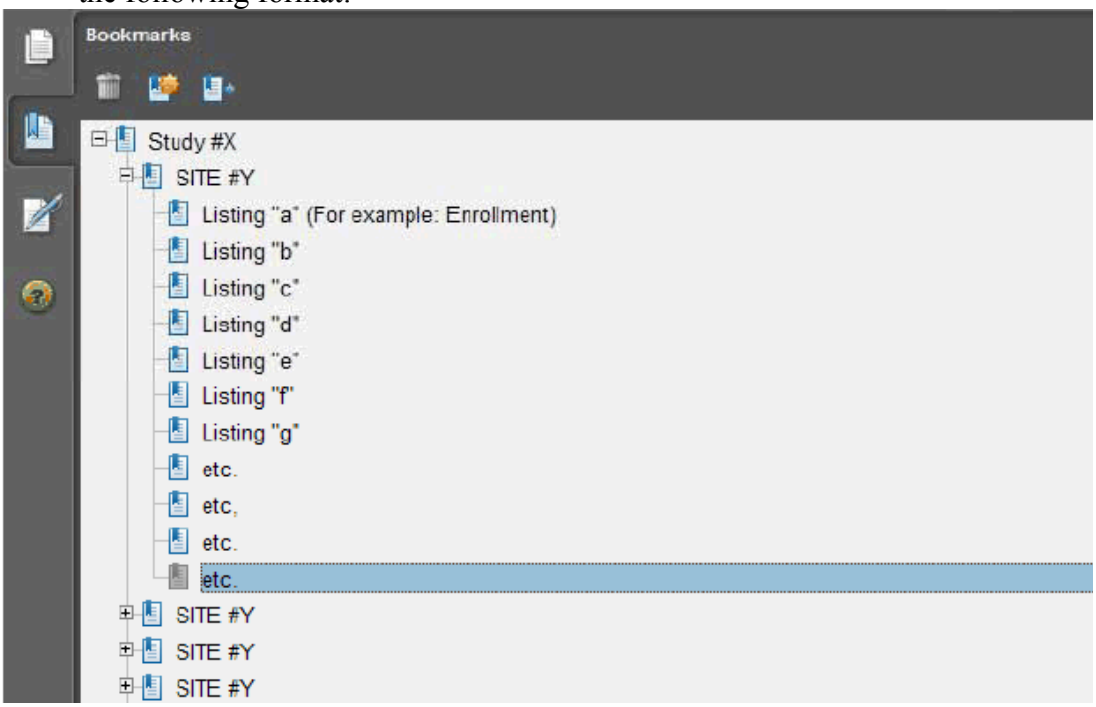
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)

c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA

inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H Dunn
01/16/2015